IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of ATTY. DOCKET NO. 067242/0107

Fumihiko WANTANABE et al.

Serial No.: 09/120,383 Group Art Unit: 1613

Filed: July 22, 1998 Examiner: Unknown

For: SULFONATED AMINO ACID DERIVATIVES AND METALLOPROTEINASE INHIBITORS CONTAINING THE SAME

SHOWING AND STATEMENT PURSUANT TO INTERFERENCE RULE 37 C.F.R. §1.608

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Further to the Request For Interference Under Rule 607 filed herewith, applicants submit the following statement pursuant to Rule 608(a).

Applicants are entitled to an effective filing date of January 23, 1996, the filing date of the Japanese priority application 30082/96. A certified translation of the priority application is enclosed as Appendix 1. Also enclosed is a certified translation of PCT/JP97/00126, from which the instant application claims priority under 35 U.S.C. §120. The PCT supports the claims as does the instant 09/120,383 application and as set forth in the Rule 607 request. The claims are supported throughout the Japanese Priority document, for example, by claims 1, 7 and 14, and page 9, first full paragraph of the priority document. Thus, the instant application is entitled to the January 23, 1996 filing date.

The effective filing date of U.S. Patent 5,756,546 is its U.S. filing date of April 12, 1997.

Since applicants' effective filing date of January 23, 1996 is earlier than the April 12, 1997 effective filing date of the patent, applicants are *prima facie* entitled to a judgement

relative to the patentee. Therefore, it is respectfully requested that an interference be declared.

Moreover, because applicants have an earlier effective filing date, they should be designated as senior party in the interference.

Should the Examiner have any questions, he or she is invited to contact the undersigned.

Respectfully submitted,

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May 14, 1999
Date

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PTO-850 (Rev. 09-10-96)

INTERFERENCE INITIAL MEMORANDUM

Count #_____

BOARD OF PATENT APPEALS AND INTERFERENCES: An interference is found to exist between the following cases:

This interference involves 2 parties

PARTY	APPLICATION NO.	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
Watanabe et al.	09/120,383	July 22, 1998		

If application has been patented, have maintenance fees been paid? ___Yes ___No ___Maintenance fees not due yet

**Accorded the benefit of: COUNTRY	APPLICATION NO.	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
JAPAN	8/30082	January 23, 1996		
JAPAN	8/213555	August 13, 1996		
PCT	JP97/00126	January 22,1997		

The claim(s) of this party which correspond(s) to this count is(are):
PATENTED OR PATENTABLE PENDING CLAIMS: 26-32
UNPATENTABLE PENDING CLAIMS:

The claim(s) of this party which does(do) not correspond to this count is(are):
PATENTED OR PATENTABLE PENDING CLAIMS:
UNPATENTABLE PENDING CLAIMS:

PARTY	APPLICATION NO.	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
O'Brien et al.	844,598	April 21, 1997	5,756,545	May 26, 1998

If application has been patented, have maintenance fees been paid? ___Yes ___No ___Maintenance fees not due yet

**Accorded the benefit of: COUNTRY	APPLICATION NO.	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY

The claim(s) of this party which correspond(s) to this count is(are):
PATENTED OR PATENTABLE PENDING CLAIMS: 1-18
UNPATENTABLE PENDING CLAIMS:

The claim(s) of this party which does(do) not correspond to this count is(are):
PATENTED OR PATENTABLE PENDING CLAIMS:
UNPATENTABLE PENDING CLAIMS:

Instructions

1. For every patent involved in the interference, check if the maintenance fees have been paid by using the patent number with PALM screen 2970. If fees are due and they have not been paid, the interference cannot be declared since it would involve an expired patent (35 USC 135(a); 37 CFR 1.606).
2. For each party, identify the patentable (or patented) and unpatentable (pending) claims which correspond to the count (37 CFR 1.601(f), (n); 1.609(b)(2)).
3. For each party, identify the patentable (or patented) and unpatentable (pending) claims which do not correspond to the count (37 CFR 1.609(b)(3)).
4. Forward all files including those the benefit of which is being accorded.
5. Keep a copy of the Interference Initial Memorandum and any attachments for your records.

All information requested below must be attached on (a) separate typewritten sheet(s).

6. On a separate sheet, set forth a single proposed interference count. If any claim of any party is exactly the same word for word as this count, please indicate the party, application or patent number, and the claim number.
7. For each claim designated as corresponding to the count, provide an explanation of why each claim defines the same patentable invention as the count (37 CFR 1.609(b)(2)).
8. For each claim designated as not corresponding to the count, provide an explanation of why each claim defines a separate patentable invention from the count (37 CFR 1.609(b)(3).
9. For each additional count, if any, repeat steps 2-6 and, additionally, provide an explanation why each count represents a separate patentable invention from every other count (37 CFR 1.609(b)(1).

DATE	PRIMARY EXAMINER (Signature)	TELEPHONE NO.	ART UNIT
DATE	GROUP DIRECTOR SIGNATURE (if required)		

**The application number and filing date of each application the benefit of which is intended to be accorded must be listed. It is not sufficient to merely list the earliest application if there are intervening applications necessary for continuity.

THIS PAGE CAN BE DUPLICATED IF THERE ARE MORE THAN TWO INTERFERING PARTIES.

APPENDIX "1"

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ９７／００１２６ －

A.　発明の属する分野の分類（国際特許分類（ＩＰＣ））

Int. Cl' C07C311/00, C07D209/42, C07D213/55, C07D235/24, C07D257/04, C07D277/56, C07D277/82, C07D263/56, C07D307/91, C07D333/34, C07D333/62, A61K31/40, A61K31/535/A61K31/42, A61K31/425, A61K31/415, A61K31/44, A61K31/34, A61K31/38, A61K31/41, A61K31/18

B.　調査を行った分野

調査を行った最小限資料（国際特許分類（ＩＰＣ））

Int. Cl' C07C311/00, C07D209/42, C07D213/55, C07D235/24, C07D257/04, C07D277/56, C07D277/82, C07D263/56, C07D307/91, C07D333/34, C07D333/62, A61K31/40, A61K31/535/A61K31/42, A61K31/425, A61K31/415, A61K31/44, A61K31/34, A61K31/38, A61K31/41, A61K31/18

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAS ONLINE

C.　関連すると認められる文献

引用文献のカテゴリー＊		引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X	①	JAN-GERD HANSEL et al,'Oxazoline Formation via a Pd-catalyzed Cyclization', Tetrahedron Lett. (1995), Vol. 36, No. 17, P. 2916-2913	4, 21
X	②	S. NATELSON et al,'Preparation of D-, DL-, and L-Homoserine Lactone from Methionine', Microchem. J. (1989), Vol. 40, No. 2, P. 226-232	4, 21
X	③	N. YAMADA et al,'Reaction of L-. alpha. -tosylamid-. beta. -propiolactone. I. Synthesis, reactions with amines, and derivation to L-Ser.', 薬学雑誌(1969), Vol. 89, No. 1, P. 98-103	4, 21
X	④	S. H. LEE et al,'Systematic Study on the Resolution of derivatized amino acids enan-tiomers on different cyclodextrin-bonded stationary phases', J. Chromatogr. (1992), Vol. 603, No. 1-2, P. 83-93	4, 5, 20, 22
○ X	⑤	EP, 468231, A2(エフ　ホフマン-ラ　ロシュ　アーゲー) 29. 1月. 1992 (29. 01. 92)&AU, 9179490, A & CA, 2044636, A&DE, 59103021, B&ES, 2061123, B&FI, 9103282, A&IL, 98690, A&NO, 177704, A&NZ, 238773, A&PT, 98221, A&TW, 201303, A&US, 5583133, A	4, 5, 8, 9, 14, 19, 20, 22

☒ C欄の続きにも文献が列挙されている。　　☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー

「A」特に関連のある文献ではなく、一般的技術水準を示すもの

「E」先行文献ではあるが、国際出願日以後に公表されたもの

「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）

「O」口頭による開示、使用、展示等に言及する文献

「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献

「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの

「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの

「Y」特に関連のある文献であって、当該文献と他の１以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの

「&」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
１９．０３．９７	01.04.97

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）	
日本国特許庁（ＩＳＡ／ＪＰ） 郵便番号１００ 東京都千代田区霞が関三丁目４番３号	渡辺　陽子　印	４Ｈ　９２７９
	電話番号　０３－３５８１－１１０１　内線　３４４３	

様式ＰＣＴ／ＩＳＡ／２１０（第２ページ）（１９９２年７月）

国際調査報告

国際出願番号 PCT／JP97／00126

C（続き）. 関連すると認められる文献

引用文献のカテゴリー＊	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
X ⑥	A. K. DEBNATH et al, '4-(4'-Substituted benzoyl)aminobenzenesulphonyl-L(+)-gl-utamicacids and 5-N-substituted-2-[4'-(4"-substituted benzoyl)aminobenzenes-ulphon-yl]-L-glutamines as potential antineoplastic agents', Indian J. Chem., Sect. B(1989), Vol. 28B, No. 10, P. 843-847	4, 11, 16
X ⑦	V. STOCCHI et al, 'Reserved-Phase High-Performance Liquid Chromatography Separation of Dimethylaminoazobenzene Sulfonyl', Anal. Biochem. (1989), Vol. 178, No. 1, P. 107-117	4
X ⑧	L. J. KUN et al, 'Debsyl Chloride:its synthesis, characterization and application and application in amino acid and amine microanalysis', J. Chin. Biochem. Soc. (1985), Vol. 14, No. 1, P. 10-19	4, 22
X ⑨	J. HLAVACEK et al, 'An Alternative Route to N-Methylamino acid derivatives', Collect Czech. Chem. Commun. (1988), Vol. 53, No. 11A, P. 2473-2493	4, 20, 21
X ⑩	WO, 93/14069, A (ブリティッシュ・バイオテクノロジー リミテッド) 22. 7月. 1993 (22. 07. 93) &AU, 9332612, A&EP, 620813, A	4, 22
X ⑪	B. GALLI et al, 'Enantiomeric separation of dansyl-and dabsylamino acids by ligand- exchange chromatography', J. Chromatogr., A(1994), Vol. 666, No. 1-2, P. 77-89	4, 22
X ⑫	JP, 57-59969, A (ベーリンガー株式会社) 10. 4月. 1982 (10. 04. 82), 実施例1, (ファミリーなし)	4
X ⑬	M. VERDERAME et al, 'Sulfide Derivatives of Cysteine II', J. Pharm. Sci. (1962), Vol. 51, P. 576-579	4, 5
X ⑭	C. KAISER et al, '2-Substituted Derivatives of 3, 4-Dihydroxyphenylalanine', J. Am. Chem. Sci. (1957), Vol. 79, P. 4365-4370	4, 21
X ⑮	D. DUWEL et al, 'Carboxylic acid analogues of suramin, potential filaricides', Indian J. Chem., Sec. B(1991), Vol. 30B, No. 2, P. 182-187	4, 6, 11, 16
A ⑯	WO, 96/00214, A1 (チバガイギー AG) 04. 1月. 1996 (04. 01. 96) &ZA, 9505206, A &AU, 9525369, A	1-25
A ⑰	WO, 95/35276, A1 (ブリティッシュ バイオテク ファーマシューティカルズ リミテッド) 28. 12月. 1995 (28. 12. 95) &AU, 9527466, A	1-25

PATENT OFFICE
JAPANESE GOVERNMENT

This is to certify that the annexed is a true copy of the following application as filed with this office.

Date of Application: January 23, 1996
Application Number: Application No. 30082/1996
Applicant(s): Shionogi & Co.,Ltd.

Commissioner,
Patent Office Hisamitsu ARAI

【Name of Document】 PETITION

【Docket No.】 A005530

【Filing Date】 January 23, 1996

【Addressee】 Commissioner, Patent Office

【International Patent Classification】 C07C 311/19
A61K 31/18

【Title of Invention】 SULFONATED AMINO ACID DERIVATIVES, AND METALLOPROTEINASE INHIBITORS CONTAINING THE SAME

【Number of Claims】 19

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【Identification No.】 100103230

【Patent Attorney】

【Name】 Hirotsugu TAKAYAMA

【Telephone number】 06-202-2161

【List of Attached Documents】

【Item】 Specification 1

【Item】 Abstract 1

【General Authorization No.】 9505451

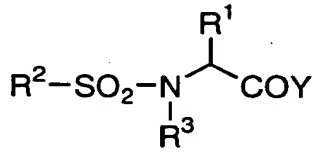
【Document's Name】 Specification

【Title of the invention】 SULFONATED AMINO ACID DERIVATIVES AND METALLOPROTEINASE INHIBITORS CONTAINING THE SAME

【Claims】

【Claim 1】 A composition for inhibiting metalloproteinase which contains a compound of the formula (I):

【Formula 1】



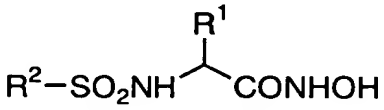
(I)

wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^2 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, or optionally substituted amino; R^3 is hydrogen atom, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and Y is -NHOH or -OH; provided R^3 is hydrogen atom when Y is -NHOH, its pharmaceutically acceptable salt, or hydrate thereof.

【Claim 2】 A composition for inhibiting metalloproteinase of claim 1 which is a composition for inhibiting type-IV collagenase.

【Claim 3】 A compound of the formula (Ia):

【Formula 2】

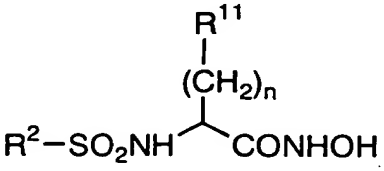


(Ia)

wherein R^1 and R^2 are as defined above, its pharmaceutically acceptable salt, or hydrate thereof.

【Claim 4】 A compound of the formula (Ib) of claim 3:

【Formula 3】



(Ib)

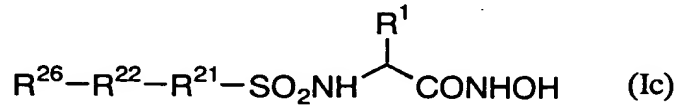
wherein R^{11} is optionally substituted aryl or optionally substituted heteroaryl; n is an integer of 0 to 6; and R^2 is as defined above.

【Claim 5】 A compound of claim 4 wherein R^{11} is optionally substituted phenyl, optionally substituted naphthyl, optionally substituted thiazolyl, optionally substituted indolyl, optionally substituted benzothiazolyl, or optionally substituted benzimidazolyl.

【Claim 6】 A compound of claim 3 wherein R^1 is isopropyl, isobutyl, or sec-butyl.

【Claim 7】 A compound of the formula (Ic) of claim 3:

【Formula 4】

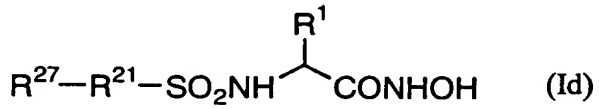


(Ic)

wherein R^{21} is phenylene, naphthylene, or thiophen-diyl; R^{22} is a bond, ethynylene, -(CH_2)m-, -N=N-, -O-, -S-, -$N(R^{23})$-, -CO-, -$N(R^{24})CON(R^{25})$-, or tetrazol-diyl; R^{26} is optionally substituted phenyl, optionally substituted naphthyl, or optionally substituted heteroaryl; m is 1 or 2; R^{23}, R^{24}, and R^{25} are each independently hydrogen atom or alkyl; and R^1 is as defined above.

【Claim 8】 A compound of the formula (Id) of claim 3:

【Formula 5】



(Id)

wherein R^{27} is hydrogen atom, halogen, acyloxy, hydroxy, carboxy, alkoxycarbonyl, alkoxy, alkyl, trifluoromethyl, nitro, or -$N(R^{28})R^{29}$; R^{28} and R^{29} are each independently hydrogen atom or alkyl; R^1 and R^{21} are as defined above.

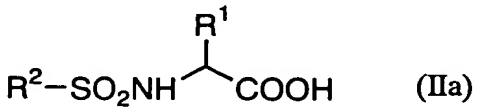
【Claim 9】 A compound of claim 7 wherein R^{21} is phenylene or thiophen-diyl; R^{22} is a bond, -CH_2-, ethynylene, -N=N-, -O-, or tetrazolyl; and R^{26} is optionally substituted phenyl.

【Claim 10】 A compound of claim 8 wherein R^{21} is phenylene or thiophen-diyl.

【Claim 11】 A compound of claim 3 wherein R^2 is optionally substituted alkyl.

【Claim 12】 A compound of the formula (IIa):

【Formula 6】

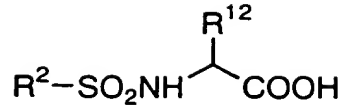


(IIa)

wherein R^1 and R^2 are as defined above, its pharmaceutically acceptable salt, or hydrate thereof.

【Claim 13】 A compound of the formula (IIb) of claim 12:

【Formula 7】

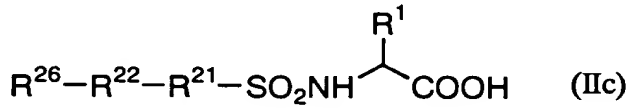


(IIb)

wherein R^{12} is phenyl, phenethyl, isopropyl, isobutyl, sec-butyl, optionally substituted thiazolylmethyl, optionally substituted naphthylmethyl, optionally substituted pyridylmethyl, optionally substituted benzothiazolylmethyl, optionally substituted benzimidazolylmethyl, indolyl substituted with alkyl, acyl, alkoxy, or halogen, alkyl substituted with halogen, cycloalkyl, carboxy, or benzyloxy, or benzyl substituted with nitro, halogen, carboxy, or phenyl; and R^2 is as defined above.

【Claim 14】 A compound of the formula (IIc) of claim 12:

【Formula 8】

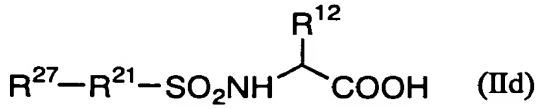


(IIc)

wherein R^1, R^{21}, R^{22}, and R^{26} are as defined above.

【Claim 15】 A compound of the formula (IId) of claim 13:

【Formula 9】



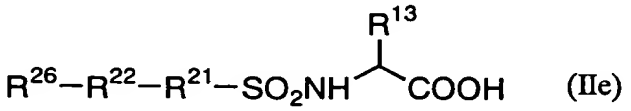
(IId)

wherein R^{12}, R^{21}, and R^{27} are as defined above.

【Claim 16】 A compound of claim 14 wherein R^{21} is phenylene or thiophen-diyl; R^{22} is a bond, -CH_2-, ethynylene, -N=N-, -O-, or tetrazolyl; and R^{26} is optionally substituted phenyl.

【Claim 17】 A compound of the formula (IIe) of claim 14:

【Formula 10】



(IIe)

wherein R^{13} is optionally substituted benzyl, optionally substituted phenethyl, optionally substituted naphthylmethyl, optionally substituted indolylmethyl, or optionally substituted alkyl; and R^{21}, R^{22} and R^{26} are as defined above.

【Claim 18】 The compound of any one of claims 3 to 17, wherein a configuration of asymmetric carbon atom bonding with R^1 is R configuration.

【Claim 19】 A composition for inhibiting type IV collagenase which contains the compound of any one of claims 3 to 17.

【Detailed Description of Invention】

【0001】

【Field of Industrial Application】

This application relates to sulfonated amino acid derivatives and metalloproteinase inhibitors containing the same.

【0002】

【Prior Art】

An extracellular matrix consists of collagen, proteoglycan, etc., has a function to support tissues, and plays a role in a maintaining of a cell functions , for example propagation, differentiation, adhesion, or the like. Matrix metalloproteinases (MMP) such as gelatinase, stromelysin, collagenase, and the like have an important role in degradation of an extracellular matrix, and these enzymes work for growth, tissue remodeling, etc. under physiological conditions. Therefore, it is considered that these enzymes participate in progression of various kind of diseases involving breakdown and fibrosis of tissues, such as osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontitis, metastasis and invasion of tumor, and virus infection (for example, HIV infection). At the present time, it is not clear which enzyme participates in the above diseases seriously, but it is considered that these enzymes at least participate in tissue breakdown. N-substituted sulfonamide derivatives of hydroxamic acid derivatives of amino acids are described in JP-A-6-256293. However, N-sulfonated amino acid derivatives having activity for inhibiting metalloproteinase of the present invention are not reported .

【0003】

【Problems to be solved by the Invention】

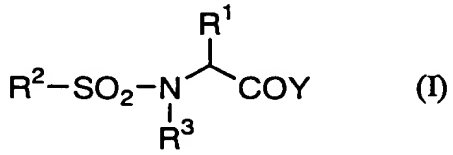
If it is able to inhibit the activity of MMP, it is considered that MMP inhibitors contribute to an improvement and prevention of the above diseases caused by or related to its activity. Therefore, development of MMP inhibitors has long been desired.

【0004】

【Means to Solve the Problems】

In the above situation, the inventors of the present invention found that a compound of formula (I):

【Formula 11】



(I)

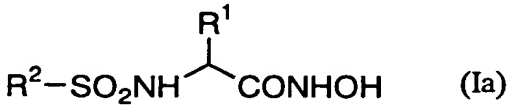
wherein R^1 is optionally substituted lower alkyl, optionally substituted aryl, optionally

substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; R^2 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, or optionally substituted amino; R^3 is hydrogen atom, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroarylalkyl; and Y is -NHOH or -OH; provided R^3 is hydrogen atom when Y is -NHOH, its pharmaceutically acceptable salt, or hydrate thereof has activity for inhibiting metalloproteinase and significantly inhibit the growth lung cancer cells. It is also found that it is more stable against racemization than conventional sulfonated amino acid derivatives.

【0005】

Concretely, the compound of the present invention includes a compound of the formula (Ia):

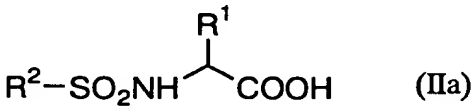
【Formula 12】



(Ia)

wherein R^1 and R^2 are as defined above and (2)-2 a compound of the formula (IIa):

【Formula 13】

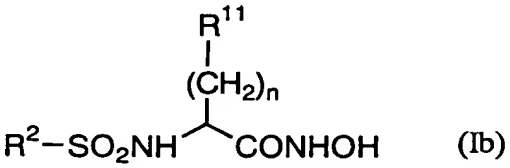


(IIa)

wherein R^1 and R^2 are as defined above.

As a preferable mode, (2)-1 (A) a compound of the formula (Ib):

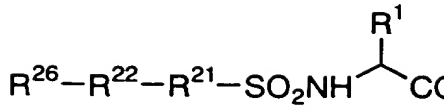
【Formula 14】



(Ib)

wherein R^{11} is optionally substituted aryl or optionally substituted heteroaryl; n is an integer of 0 to 6; and R^2 is as defined above is exemplified and as a particularly preferable mode, a compound wherein R^{11} is optionally substituted phenyl, optionally substituted naphthyl, optionally substituted thiazolyl, optionally substituted indolyl, optionally substituted benzothiazolyl, or optionally substituted benzimidazolyl is exemplified. Lokewise, (C) a compound of the formula (Ic):

【Formula 15】



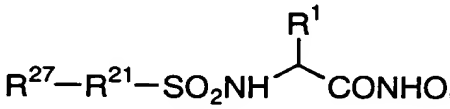
(Ic)

wherein R^{21} is phenylene, naphthylene, or thiophen-diyl; R^{22} is a bond, ethynylene, -(CH_2)m-, -N=N-, -O-, -S-, -N(R^{23})-, -CO-, -N(R^{24})CON(R^{25})-, or tetrazolyl; R^{26} is optionally substituted phenyl, optionally substituted naphthyl, or optionally substituted heteroaryl; m is 1 or 2; R^{23}, R^{24}, and R^{25} are each independently hydrogen atom or alkyl; and R^1 is as defined above is exemplified, especially, a compound wherein R^{21} is phenylene or thiophen-diyl; R^{22} is a bond, -CH_2-, ethynylene, -N=N-, -O-, or tetrazolyl; and R^{26} is optionally substituted phenyl is exemplified.

【0006】

Similarly, (D) a compound of the formula (Id):

【Formula 16】



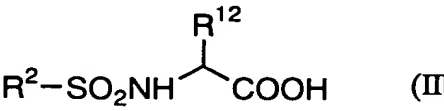
(Id)

wherein R^{27} is hydrogen atom, halogen, acyloxy, hydroxy, carboxy, alkoxycarbonyl, alkoxy, alkyl, trifluoromethyl, nitro, or -N(R^{28})R^{29}; R^{28} and R^{29} are each independently hydrogen atom or alkyl; R^1 and R^{21} are as defined above is exemplified, especially a compound wherein R^{21} is phenylene or thiophen-diyl is exemplified.

In the same way, (E) a compound of the formula (Ia) wherein R^2 is optionally substituted alkyl is exemplified.

Likewise, (2)-2 (F) a compound of the formula (IIb):

【Formula 17】

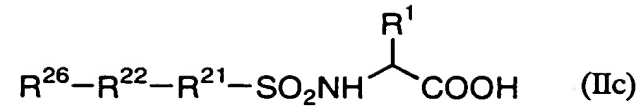


(IIb)

wherein R^{12} is phenyl, phenethyl, isopropyl, isobutyl, sec-butyl, optionally substituted thiazolylmethyl, optionally substituted naphthylmethyl, optionally substituted pyridylmethyl, optionally substituted benzothiazolylmethyl, optionally substituted benzimidazolylmethyl, indolyl substituted with alkyl, acyl, alkoxy, or halogen, alkyl substituted with halogen, cycloalkyl, carboxy, or benzyloxy, or benzyl substituted with nitro, halogen, carboxy, or phenyl; and R^2 is as defined above is exemplified, especially, a compound wherein R^2 is -R^{21}-R^{27} is exemplified.

Similarly, (G) a compound of the formula (IIc):

【Formula 18】

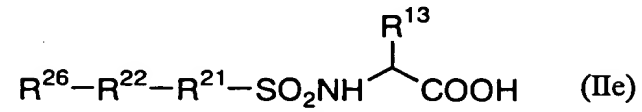


(IIc)

wherein R^1, R^{21}, R^{22}, and R^{26} are as defined above is exemplified.

In the same way, (H) a compound of the formula (IIe):

【Formula 19】



(IIe)

wherein R^{13} is optionally substituted benzyl, optionally substituted phenethyl, optionally substituted naphthylmethyl, optionally substituted indolylmethyl, or optionally substituted alkyl; and R^{21}, R^{22} and R^{26} are as defined above is exemplified.

Additionally, as a characteristic compound, a compound wherein a configuration of asymmetric carbon atom bonding with R^1 is R configuration is preferable.

【0007】

The term "alkyl" herein used means C_1-C_{10} straight or branched chain alkyl, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, i-pentyl, neo-pentyl, tert-pentyl, and the like.

【0008】

The term "alkenyl" herein used means C_2-C_{10} straight or branched chain alkenyl, for example, vinyl, allyl, i-propenyl, pentenyl (e.g., 1-pentenyl), and the like.

The term "aryl" herein used is exemplified by phenyl, naphthyl, and the like. Phenyl is preferred.

The term "aralkyl" herein used means the above mentioned alkyl substituted by the above mentioned aryl at any possible position. Examples of the aralkyl are benzyl, phenethyl, phenylpropyl (e.g., 3-phenylpropyl), naphthylmethyl (α-naphthylmethyl), anthrylmethyl (9-anthrylmethyl), and the like. Benzyl is preferred. The aryl part may optionally be substituted.

【0008】

The term "heteroaryl" herein used means a 5 to 6 membered aromatic heterocyclic group which contains one or more hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur atoms in the ring and may be fused with a carbocyclic ring or other heterocyclic ring at any possible position. Examples of the heteroaryl are pyrrolyl (e.g., 1-pyrrolyl), indolyl (e.g., 2-indolyl, 1-formylindolyl, 1-acetylindolyl), carbazolyl (e.g., 3-carbazolyl), imidazolyl (e.g., 4- imidazolyl), pyrazolyl (e.g., 1-pyrazolyl), benzimidazolyl (e.g., 2-benzimidazolyl), indazolyl (e.g., 3-indazolyl),

indolizinyl (e.g., 6-indolizinyl), pyridyl (e.g., 1-pyridyl), quinolyl (e.g., 5-quinolyl), isoquinolyl (e.g., 3-isoquinolyl), acridinyl (e.g., 1-acridinyl), phenanthridinyl (e.g., 2-phenanthridinyl), pyridazinyl (e.g., 3-pyridazinyl), pyrimidinyl (e.g., 4-pyrimidinyl), pyrazinyl (e.g., 2-pyrazinyl), cinnolinyl (e.g., 3-cinnolinyl), phthalazinyl (e.g., 2-phthalazinyl), quinazolinyl (e.g., 2-quinazolinyl), isoxazolyl (e.g., 3-isoxazolyl), benzisoxazolyl (e.g., 3-benzisoxazolyl), oxazolyl (e.g., 2-oxazolyl), benzoxazolyl (e.g., 2-benzoxazolyl), benzoxadiazolyl (e.g., 4-benzoxadiazolyl), isothiazolyl (e.g., 2-isothiazolyl), benzisothiazolyl (e.g., 2-benzisothiazolyl), thiazolyl (e.g., 2-thiazolyl), benzothiazolyl (e.g., 2-benzothiazolyl), furyl (e.g., 3-furyl), benzofuryl (e.g., 3-benzofuryl), thienyl (e.g., 2-thienyl), benzothienyl (e.g., 2-benzothienyl), tetrazolyl, and the like. The aryl part of the above heteroaryl is optionally substituted.

[0010]

The term "heteroarylalkyl" herein used means the above mentioned alkyl substituted with the above mentioned heteroaryl at any possible position. Examples of the heteroarylalkyl are thiazolylmethyl (e.g., 4-thiazolylmethyl), thiazolylethyl (e.g., 5-thiazolyl-2-ethyl), indolylmethyl (e.g., 2-indolylmethyl, 1-formylindolylmethyl, 1-acetylindolylmethyl), imidazolylmethyl (e.g., 4-imidazolylmethyl), benzothiazolylmethyl (e.g., 2-benzothiazolylmethyl), benzodiazolylmethyl (4-benzodiazolylmethyl), benzotriazolylmethyl (e.g., 4-benzotriazolylmethyl), benzoquinolylmethyl (e.g., 2-benzoquinolylmethyl), benzimidazolylmethyl (e.g., 2-benzimidazolylmethyl), pyridylmethyl (e.g., 2-pyridylmethyl), and the like. The aryl part of the above heteroaryl is optionally substituted.

[0011]

The term "halogen" herein used is exemplified by fluoro, chloro, bromo, and iodo, and the like.

The term "acyloxy" herein used is exemplified by alkanoyloxy (e.g., acetyloxy), aroyloxy (e.g., benzoyloxy), arylalkanoyloxy (e.g., phenylacetyloxy), and the like.

The term "alkoxy carbonyl" herein used is exemplified by methoxycarbonyl, ethoxycarbonyl, tert-butylcarbonyl, benzyloxycarbonyl, and the like.

The term "alkoxy" herein used is exemplified by methoxy, ethoxy, and the like.

The term "optionally substituted amino" herein used means mono- or di-substituted amino, for example, ethylamino, dimethylamino, cyclohexylamino, etc., and cyclic amino, for example, piperidino, morpholino, etc.

The term "thiophen-diyl" is exemplified by 2,5-thiophendiyl, 3,4-thiophendiyl, 3,4-thiophendiyl, and the like.

[0012]

Substituents for "optionally substituted alkyl" and "optionally substituted alkenyl" are hydroxy, alkoxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl), halogen (e.g., fluoro, chloro, bromo, and iodo), carboxy, ester form of carboxy (e.g., methoxycarbonyl and ethoxycarbonyl), nitro, cyano, trifluoromethyl, substituted or unsubstituted amino (e.g., methylamino, dimethylamino, and carbamoylamino), guanidino, phenyl, benzyloxy, and the like. These substituents are able to bind them at one or more of any possible positions.

[0013]

Substituents for the aromatic ring of "optionally substituted aralkyl (e.g., naphthylmethyl)", "optionally substituted heteroarylalkyl (e.g., optionally substituted thiazolylmethyl, optionally substituted pyridylmethyl, optionally substituted benzimidazolylmethyl)", "optionally substituted aryl (e.g., optionally substituted phenyl, optionally substituted naphthyl)", "optionally substituted heteroaryl (optionally substituted thiazolyl, optionally substituted indolyl, optionally substituted benzothiazolyl, optionally substituted benzimidazolyl)", and "optionally substituted phenylene" are, for example, hydroxy, alkoxy (e.g., methoxy and ethoxy), mercapto, alkylthio (e.g., methylthio), cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl), halogen (e.g., fluoro, chloro, bromo, and iodo), carboxy, ester form of carboxy (e.g., methoxycarbonyl and ethoxycarbonyl), nitro, cyano, trifluoromethyl, aryloxy (e.g., phenyloxy) substituted or unsubstituted amino (e.g., methylamino, dimethylamino, and diethylamino), guanidino, alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, tert-butyl, n-pentyl, i-pentyl, neo-pentyl, and tert-pentyl), alkenyl (e.g., vinylene and propenylene), alkynyl (e.g., acetylene and phenylacetylene), alkanoyl (e.g., formyl, acetyl, and propionyl), acyloxy (e.g., acetyloxy), phenyl, benzyl, imino (e.g., bezylideneamino), an azo group (e.g., phenylazo), optionally substituted heteroaryl (e.g., 3-pyridyl), optionally substituted ureido (e.g., ureido and phenylureido), and the like. These substituents are able to bind to it at one or more of any possible position.

[0014]

The term " pharmaceutically acceptable salt " herein used is exemplified by a salt with alkali metals (e.g., lithium, sodium, potassium, etc.), alkaline earth metals (e.g., calcium, magnesium, etc.), ammonium (e.g., ammonium, trimethylammonium, diethylammonium, etc.), mineral acids (e.g., hydrochloric acid, sulfuric acid, etc.), and organic acids (e.g., methanesulfonic acid, mallein acid, etc.).

The term "hydrate" herein used includes hydrates of the compound

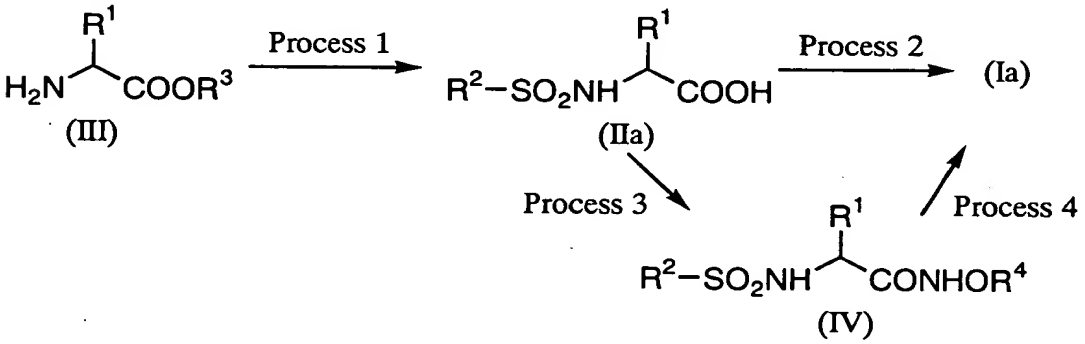
represented by the formula (I) and its pharmaceutically acceptable salt.

The compound of the present invention includes all of stereoisomers (diastereoisomer, enantioisomer, epimaer) and all of racemates. The compound wherein a configuration of asymmetric carbon atom bonding with R^1 is R configuration is preferred.

[0015]

Compounds (Ia) and (IIa) of the invention are able to be synthesized from the corresponding α-amino acids represented by the formula (III).

[Formula 20]



wherein R^1 and R^2 are as defined above, R^3 is hydrogen atom or a carboxy protective group, and R^4 is a hydroxy protective group.

Conversion of compound (III) to compound (IIa) is sulfonation of an amino group of the compound (III) (process 1). If necessary, after this reaction, N-alkylation, deprotection of a carboxyl protective group, etc. are carried out. Conversion of compound (IIa) to compound (Ia) is to obtain hydroxamic acid derivatives from carboxylic acid derivatives (process 2). To obtain compound (IIa) from compound (Ia), compound (IIa) may also be reacted with hydroxylamine having a hydroxyl protective group or its acidic salts to give compound (IV) (process 3), followed by and deprotection (process 4). Conversion to sulfonyl derivatives and hydroxamic acid derivatives are able to be carried out according to an usual method. For example, an amino acid represented by the formula (III) is reacted with a sulfonating agent such as sulfonyl halide represented by R^2-SO_2X' (R^2 is as defined above; and X' is halogen) and then hydroxylamine. Each process will hereinafter be described in more detail.

[0016]

(Process 1)

Some of amino acids represented by the formula (III) or its acidic salts (e.g., hydrochloride, p-toluenesulfonate, and trifluoroacetate) which are starting materials are commercially available. The other are able to be synthesized in accordance with a

method described in Zikkenkagakukoza, vol. 22, IV (nihonkagakukai), J. Med. Chem. 38, 1689-1700, 1995, Gary M. Ksander et. al., etc. some of sulfonating agents are commercially available and the other are synthesized in accordance with a method described Shin-zikkenkagakukoza, vol. 14, 1787, 1978, Synthesis 852-854, 1986, etc. A carboxyl protective group is exemplified by esters (e.g., methyl ester , tert-butyl ester and benzyl ester). Deprotection of this protective group may be carried out by hydrolysis with acid (e.g., hydrochloride and trifluoroacetic acid) or base (e.g., sodium hydroxide) depending on the type of the group, or by catalytic reduction, e.g., under 10% palladium-carbon catalyst condition. To obtain a compound (Ia), the esters may directly be converted to hydroxamic acid by the method of process 2. When a compound (III) is an amino acid wherein R^3 is hydrogen atom, preferable solvents for this sulfonylation are dimethylformamide, tetrahydrofuran, dioxane, dimethylsulfoxide, acetonitrile, water, or mixed solvents thereof. When a compound (III) is an amino acid wherein R^3 is a protective group such as an ester, a solvent for this sulfonylation is exemplified by the above solvents and mixed solvents of water-insoluble solvents (e.g., benzene and dichloromethane) and the above solvents. A base to be used in this sulfonylation is exemplified by organic bases such as triethylamine, N-methylmorpholine, etc. and inorganic bases such as sodium hydroxide, potassium hydroxide, potassium carbonate, and the like. Usually this reaction can be carried out at ice-cooling to room temperature. When R^1, R^2 or R^3 of compound (IIa) contains a functional group(s) possibly interfering this sulfonylation (e.g., hydroxy, mercapto, amino, and guanidino), it can previously be protected in accordance with a method described in " Protective Groups in Organic Synthesis" (Theodora W. Green (John Wiley & Sons)) and then deprotected at an appropriate process.

【0017】

(Process 2)

A hydroxylamine is reacted with compound (IIa) or its reactive derivatives to give hydroxamic acid derivatives (Ia). A hydroxylamine is usually used as its acidic salts (e.g., hydrochloride, and phosphate, sulfate: commercially available) in the presence of a base. A base to be used in this reaction is exemplified by organic bases such as triethylamine, N, N-dimethylaniline, N-methylmorpholine, etc. and inorganic bases such as sodium hydroxide, potassium hydroxide, potassium carbonate, etc. When compound (IIa) is used as a starting material of conversion to hydroxamic acid, this reaction is carried out in the presence of a peptide condensing agent (e.g., dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, N,N'-carbonyldiimidazole, or a mixture of one of the above agents with 1-

hydroxybenzotriazole, N-hydroxy sucinicimide, etc.). A solvent for this reaction may be dimethylformamide, tetrahydrofuran, dioxane, dimethylsulfoxide, acetonitrile, water, and mixed solvent thereof. This reaction is carried out at -20 ℃ to 40 ℃, preferably ice-cooling to room temperature, for 1 to 16 hours.

[0018]

Acid anhydrides (especially, mixed acid anhydrides), acid halides, acid azides, and esters can be utilized in this reaction as a reactive derivative of compound (IIa). These reactive derivatives are produced by usual methods. For example, the acid anhydride derivatives can be produced by a reaction of compound (IIa) with acid halide derivatives (e.g., ethyl chlorocarbonate) in the presence of a base (e.g., triethylamine), and acid halide derivatives can be produced by a reaction of compound (IIa) with a halogenation agent (e.g., oxalylchloride, and thionylchloride). Ester derivatives may be inactive or active. Sulfonyl derivatives converted from a compound (III) wherein R^3 is a carboxyl protective groups (e.g., methyl, tert-butyl, and benzyl) at process 1 can be used as inactive esters without deprotection. Active esters can be produced by a reaction of compound (IIa), carbodiimide reagents (e.g., dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide), and hydroxy derivatives corresponding to the active ester residue such as 1-hydroxybenzotriazole, N-hydroxysuccinimide, or the like. A reaction condition of conversion of the reactive derivatives of compound (IIa) to hydroxamic acid may be the same as that of conversion of compound (IIa) itself to hydroxamic acid . The reactions of processes 1 and 2 are able to continuously be carried out in one-pot reaction.

[0019]

(Process 3)

A protected hydroxylamine to be used in this reaction includes O-benzylhydroxylamine, O-(p-methoxybenzyl)hydroxylamine, O-(tert-butyl)hydroxylamine, or the like. This reaction condition may be in the same manner as that of process 2.

[0020]

(Process 4)

This process for deprotection is carried out by catalytic reduction, treatment with conc. hydrochloric acid, or treatment with trifluoroacetic acid to give the desired compound (Ia). The compounds of this invention (Ia) and (IIa) can be isolated and purified by usual separation methods and purification methods (e.g., chromatography, crystallization, etc.).

[0021]

The compound of the present invention represented by the formula (I) has an excellent activity for inhibiting metalloproteinase and inhibits matrix dissolution, as described in the following test examples. Therefore, the compound of the present invention is useful to treat or prevent diseases which are caused by MMP, for example, osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontal disease, metastasis and invasion of tumor, virus infection (e.g., HIV).

【0022】

The compound of the present invention can be administered by oral and parenteral administration. When the compound is administered by oral administration, usual formulations, for example, solid preparations such as tablets, powder, capsules, granules, etc., and liquid medicines such as aqueous suspension, oiliness suspension, syrup, elixir, etc. are applicable. When the compound is administered by parenteral administration, aqueous or oiliness suspending injection and rectum administering suppositorium are able to use. When the formulation is prepared, usual excipients, binders, lubricants, aqueous solutions, oily solutions, emulsifiers, suspending agents and the like are able to be used. Additionally, the formulation can contain the other auxiliaries such as preservatives, stabilizers, etc.

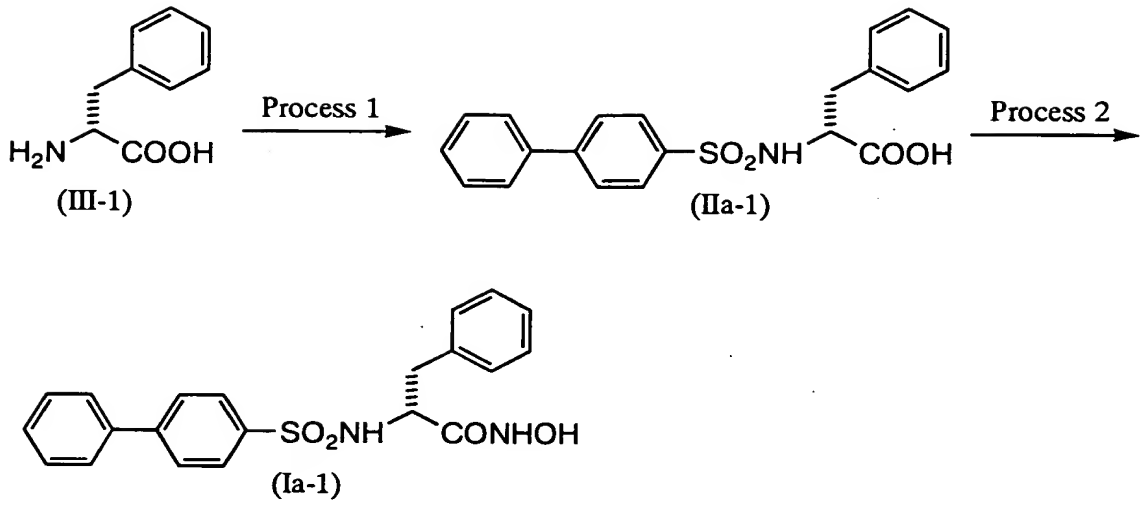
An appropriate dosage varies with the administration method, the age of the patients, their weight, their conditions and their diseases. Usually, in the case of oral administration, a daily dosage can generally be between 10 - 800 mg/kg, preferably 50 - 200 mg/kg. In the case of parenteral administration, the daily dosage can generally be between 0.1 - 200 mg/kg, preferably 1 - 100 mg/kg. The daily dosage can be administrated in 1 to 3 divisions.

The following examples are provided to further illustrate the present invention and are not to be construed as limiting the scope thereof.

【0023】

Example 1

【Formula 21】



(III-1) (IIa-1) (Ia-1)

To a suspension of (R)-(+)-phenylalanine (compound III-1, 1.65g (10 mmol)) in 50 ml of dimethylformamide and 35 ml of water was stirred and treated with 2.78 ml (20 mmol) of triethylamine under ice-cooling. Then, 2.52g(10 mmol) of 4-biphenylsulfonyl chloride in 10 ml of dimethylformamide was added dropwise to the mixture over 5 min. After the reaction mixture was stirred for 2 h at the same temperature, 1.35 g (10 mmol) of 1-hydroxybenzotriazole hydrate, 2.1 g (11 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 3.47 g (50 mmol) of hydroxylamine hydrochloride, and 7 ml (50 mmol) of triethylamine were added to the mixture. After being stirred for 16 h at room temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 2N HCl, 5% $NaHCO_3$, and water, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with $CHCl_3$ / MeOH = 40/1 to 20/1 were collected to yield 1.70 g of compound (Ia-1) as a foam. Yield 43%. mp. 169-170℃.

Elemental analysis (%) $C_{21}H_{20}N_2O_4S$

Calcd. : C; 63.62, H; 5.08, N; 7.07, S; 8.09

Found : C;63.61, H; 5.12, N; 6.98, S; 8.06

IR ν max (cm^{-1}) (Nujol) : 3365, 3295, 3266, 1674, 1320, 1159.

NMR (δ ppm) d_6-DMSO : 2.61 (dd, J=8.6, 13.4Hz, 1H), 2.80 (dd, J=6.0, 13.6Hz, 1H), 3.80 (m, 1H).

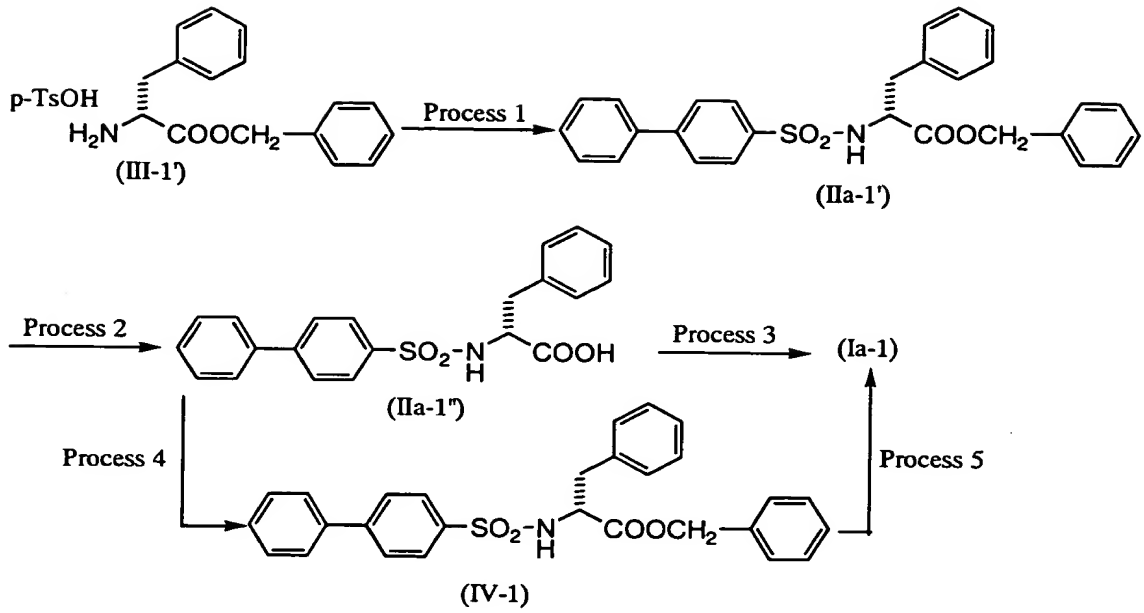
$[\alpha]_D$: +18.5±1.2 (c=0.503 %, 25℃, DMSO)

【0024】

Example 1'

Another synthetic method of compound (Ia-1)

【Formula 22】



Process 1

To a solution of (R)-phenylalanine benzyl ester tosylate (compound XV-1', 2.5 g (5.85 mmol)) in 60 ml of dichloromethane was added triethylamine (1.8 ml, 12.87 mmol) and 4-biphenylsulfonyl chloride(1.63 g, 6.44 mmol) under ice-cooling. After being stirred for 2 h at room temperature, the reaction mixture was washed with 2N HCl, 5% $NaHCO_3$ and water, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with $CHCl_3$ / MeOH = 40/1 to 20/1 were collected and crystallized from dichloromethane / hexane to give 2.32 g of compound (Ia-1-1'). Yield 84.1%. mp. 130-131℃.

Elemental analysis (%) $C_{28}H_{25}NO_4S$

Calcd. : C; 71.32, H; 5.34, N; 2.97, S; 6.80

Found : C; 71.05, H; 5.41, N; 3.00, S; 6.81

IR ν max (cm^{-1}) (Nujol) : 3352, 1732, 1341, 1190, 1163.

NMR (δ ppm) ($CDCl_3$): 3.06 (d, J=5.8Hz, 2H), 4.30 (dt, J=6.0, 9.0Hz, 1H), 4.89 (s, 2H), 5.12 (d, J=9.0Hz, 1H), 6.98-7.81 (m, 14H).

$[\alpha]_D$: -16.4±1.1(c=0.506 %, 25℃, MeOH)

【0025】

Process 2

A solution of compound (III-1') (2.28 g) which was obtained process 1 in 50 ml of mixed solvents of methanol / ethyl acetate =1/1, was hydrogenated using 10 % Pd/C (200 mg) for 25 min. The reaction mixture was filtered off, and the filtrate was concentrated in vacuo. The residue was recrystallized from dichloromethane / hexane

to give 1.83 g of compound (IIa-1"). Yield 99.1 %. mp. 146-147℃.

Elemental analysis (%) $C_{21}H_{19}NO_4S$

Calcd.: C; 66.12, H; 5.02, N; 3.67, S; 8.41

Found: C;65.97, H; 5.06, N; 3.61, S; 8.48

IR ν max (cm^{-1}) (Nujol) : 3408, 3305, 1751, 1325, 1161, 1134.

NMR (δ ppm) ($CDCl_3$): 2.97 (dd, J=7.0, 13.8Hz, 1H), 3.14 (dd, J=5.2, 14.0Hz,1H), 4.13 (m, 1H), 7.03-7.78 (m, 14H).

$[\alpha]_D$: -4.0±0.4(c=1.000 %, 25℃, MeOH)

【0026】

Process 3

To a solution of compound (IIa-1", 1.0 g (2.62 mmol)) which was obtained process 2 in dichloromethane (20 ml) was added 0.33 ml (3.93 mmol) of oxalyl chloride and one drop of dimethylformamide. After being stirred for stirred for 1 h at room temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in 10 ml of tetrahydrofuran. A solution of hydroxylamine hydrochloride (911 mg (13.1 mmol)) and $NaHCO_3$ 1.54 g (18.34 mmol) in 10ml of tetrahydrofuran and 10ml of water was stirred for 5 min under ice-cooling. To the mixture was added the above solution of acid chloride in tetrahydrofuran and the resulting mixture was stirred for 30 min. The reaction mixture was poured into water, and extracted with ethyl acetate. The organic layer was washed with 5% $NaHCO_3$, and water, and concentrated in vacuo to give compound (Ia-1) (969 mg). Yield 93.3 %.

【0027】

Process 4

To a solution of compound (IIa-1", 2.0 g, 5.24 mmol) which was obtained process 2 in dimethylformamide (20 ml) was added 1-hydroxybenzotriazole hydrate (0.7 g, 5.24 mmol), N-methylmorpholine (2.9 ml, 26.2 mmol), 1-ethyl-3-(3-diisopropylamino) carbodiimide hydrochloride (8 mmol), and O-benzylhydroxylamine hydrochloride (1.67 g, 10.48 mmol), and the resulting mixture was stirred for 6 h at room temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 2N HCl, 5% $NaHCO_3$, and water, and concentrated in vacuo. The residue was subjected to silica gel column chromatography and the fractions eluting with CH_2Cl_2 / hexane = 1/1 were collected and recrystallized from dichloromethane / hexane to give 2.04 g of compound (IV-1). Yield 80 %. mp. 171-173℃.

Elemental analysis (%) $C_{28}H_{26}N_2O_4S$

Calcd.: C; 69.12, H; 5.39, N; 5.76, S; 6.59

Found :C; 68.85, H; 5.46, N; 5.76, S; 6.78

IR ν max (cm^{-1}) (Nujol) : 3248, 1661, 1594, 1333, 1163.

NMR (δ ppm) ($CDCl_3$): 2.85-3.60 (m, 2H), 3.86 (m, 1H), 4.77 (ABq-Apart, J=11.4Hz, 1H), 4.82 (ABq-Bpart, J=11.4Hz, 1H), 5.00 (m, 1H), 6.95-7.70 (m, 19H).

$[\alpha]_D$: -40.2±1.6 (c=0.505 %, 25℃, DMSO)

【0028】

Process 5

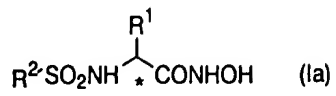
A solution of compound (IV-1) (1.97 g) which was obtained process 4 in a 60 ml of mixed solvents of methanol / ethyl acetate =1/1 was hydrogenated using 10 % Pd-C (200 mg) for 3.5 h. The reaction mixture was filtered off, and the filtrate was concentrated in vacuo. The residue was recrystallized from dichloromethane / hexane to give 1.35 g of compound (Ia-1). Yield 84.4 %.

【0029】

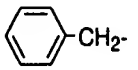
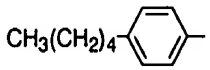
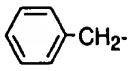
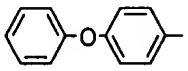
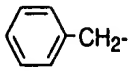
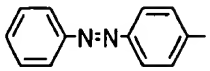
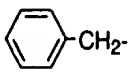
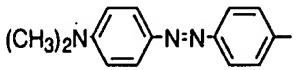
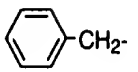
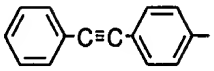
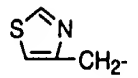
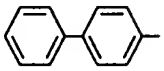
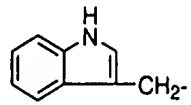
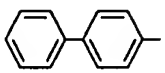
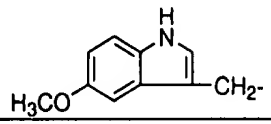
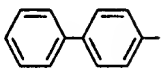
Example 2 - 58

The compounds which were shown in Tables 1 to 26 were synthesized in a manner similar to those described in Example 1'.

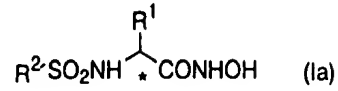
[Table 1]



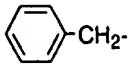
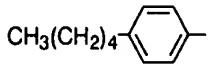
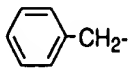
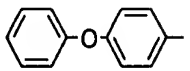
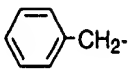
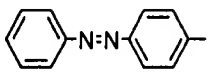
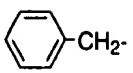
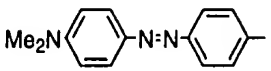
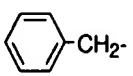
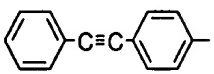
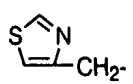
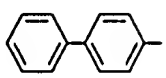
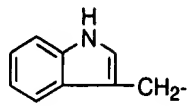
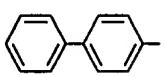
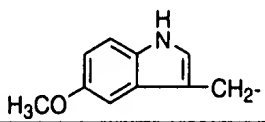
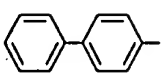
(Ia)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
2			R	129-131	$C_{20}H_{26}N_2O_4S$ Calc. C;61.52 H;6.71 N;7.17 S;8.21 Foun.C;61.87 H;6.74 N;6.83 S;7.87
3			R	foam	$C_{21}H_{20}N_2O_5S \cdot 00.2H_2O$ Calc. C;60.62 H;4.94 N;6.73 S;7.71 Foun.C;60.54 H;4.95 N;6.58 S;7.59
4			R	157-160	$C_{21}H_{20}N_4O_4S \cdot 00.6H_2O$ Calc. C;58.06 H;4.74 N;12.81 S;7.19 Foun.C;57.95 H;4.91 N;12.87 S;7.37
5			R	138-142	——
6			R	156-158	$C_{23}H_{20}N_2O_4S$ Calc. C;65.70 H;4.79 N;6.66 S;7.63 Foun.C;65.31 H;5.00 N;6.40 S;7.62
7			RS	173 >	$C_{18}H_{17}N_3O_4S_2$ Calc. C;53.38 H;4.25 N;10.41 S;15.89 Foun.C;53.36 H;4.42 N;10.36 S;15.64
8			R	203-206	$C_{23}H_{21}N_3O_4S \cdot 00.1CHCl_3$ Calc. C;62.01 H;4.75 N;9.39 S;7.17 Foun.C;62.27 H;4.89 N;9.70 S;6.75
9			RS	——	——

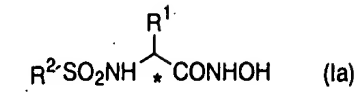
[Table 2]



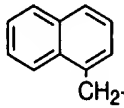
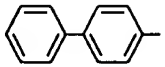
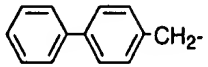
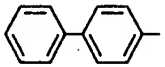
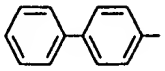
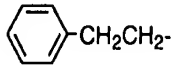
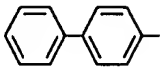
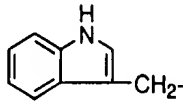
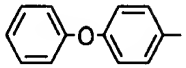
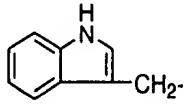
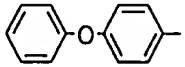
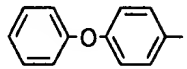
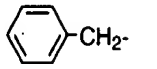
(Ia)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
2			R	3700-2400br,3247, 1636,1337,1160	0.90(t,J=6.8Hz,3H),1.22-1.40(m,4H),1.52-1.67(m,2H),2.62(t,J=7.7Hz,2H),2.86(dd,J=8.4,13.7Hz,1H),3.02(dd,J=5.7,13.7Hz,1H) ($CDCl_3$)
3			R	3700-2400br,3277, 1669,1325,1152	2.60(dd,J=8.7,13.7Hz,1H), 2.79(dd, J=6.0,13.7Hz,1H),3.75(ddd,J=6.0, 8.7,9.0,1H),6.94(d,J=8.9Hz.2H)
4			R	3700-2400br,3273, 1633,1338,1166	2.65(dd,J=8.9,13.6Hz,1H), 2.82(dd, J=6.6,13.6Hz,1H),3.86(m,1H),7.75 (d,J=7.8Hz,2H),7.87(d,J=8.7Hz,2H)
5			R	3700-2400br,2921, 1672,1314,1165,	2.62(dd,J=8.6,13.5Hz,1H),2.81(dd,J=6.5,13.6Hz,1H),3.09(s,6H),3.83(m,1H),6.86(d,J=9.0Hz,2H),7.83(d,J=8.8Hz,2H)
6			R	3700-2400br,3267, 2217,1671,1321,1161	2.62(dd,J=8.4,13.5Hz,1H), 2.80(dd, J=6.0,13.5Hz,1H),3.82(ddd,J=6.0, 8.4,8.7Hz,1H),8.38(d,J=8.7Hz,1H)
7			RS	3258,1650,1377, 1348,1163 (Nujol)	2.87(dd,J=5.6,14.2Hz,1H), 2.98(dd, J=8.4,14.2Hz,1H),4.02(dd,J=2.2, 8.6Hz,1H), 7.24(d,J=2.0Hz,1H), 8.83(d,J=2.2Hz,1H)
8			R	3403,3386,3265,1673 ,1320,1162 (Nujol)	2.72(dd,J=7.2,13.8Hz,1H), 2.97(dd, 7.0,14.8Hz,1H),3.81(m,1H),
9			RS	—	—

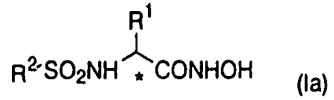
[Table 3]



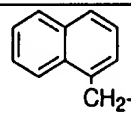
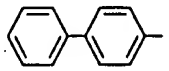
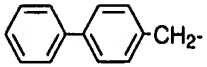
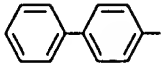
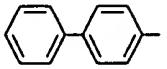
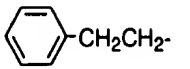
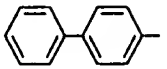
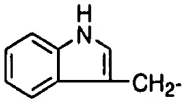
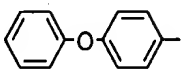
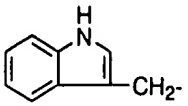
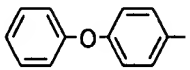
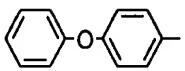
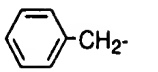
(Ia)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
10			RS	124-126	$C_{25}H_{22}N_2O_4S \cdot 00.6H_2O$ Calc. C;65.66 H;5.11 N;6.13 S;6.72 Foun.C;65.63 H;5.40 N;6.15 S;7.01
11			R	139-141	$C_{27}H_{24}N_2O_4S \cdot 00.9H_2O$ Calc. C;66.05 H;5.32 N;5.73 S;6.56 Foun.C;66.38 H;5.42 N;5.72 S;6.29
12	CF_3CH_2-		R	167-169	$C_{16}H_{15}N_2F_3O_4S \cdot 00.3H_2O$ Calc. C;48.80 H;3.99 N;7.11 F;14.47 S;8.14 Foun.C;48.77 H;3.93 N;7.08 F;14.50 S;8.11
13			RS	172-173	$C_{22}H_{22}N_2O_4S \cdot 00.1H_2O$ Calc. C;64.09 H;5.43 N;6.79 S;7.78 Foun.C;64.14 H;5.59 N;6.95 S;7.94
14			R	115-118	$C_{23}H_{21}N_3O_5S \cdot 00.1C_6H_6$ Calc. C;61.71 H;4.74 N;9.15 S;6.98 Foun.C;61.44 H;4.96 N;8.71 S;6.65
15			S	——	$C_{23}H_{21}N_3O_5S$ Calc. C;61.19 H;4.69 N;9.31 S;7.10 Foun.C;60.80 H;4.72 N;8.85 S;7.05
16	$(CH_3)_2CH$-		R	149-151	$C_{17}H_{20}N_2O_5S$ Calc. C;56.03 H;5.53 N;7.69 S;8.80 Foun.C;55.83 H;5.62 N;7.93 S;8.65
17		$CH_3(CH_2)_7$—	R	oil	$C_{17}H_{28}N_2O_4S \cdot 00.2H_2O$ Calc. C;56.71 H;7.95 N;7.78 S;8.90 Foun.C;56.60 H;7.96 N;7.90 S;8.87

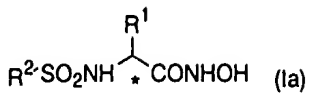
[Table 4]



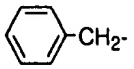
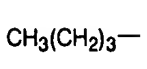
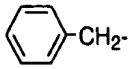
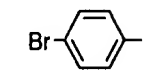
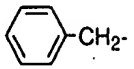
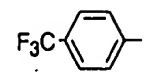
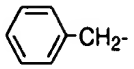
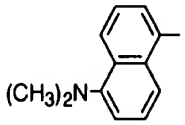
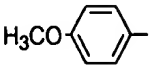
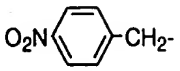
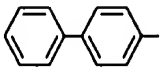
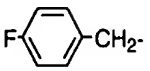
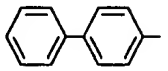
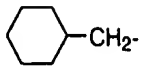
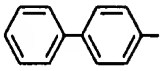
(Ia)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
10			RS	3277,1669,1397, 1322,1159,	3.12(dd,J=10.3,14.3Hz,1H), 3.89(dd, J=3.3,13.5Hz,1H),4.20(m,1H), 5.90 (brs,1H)
11			R	3262,1663,1322, 1157,	2.67(dd,J=9.2,13.1Hz,1H), 2.84(dd, J=5.3,13.5Hz,1H),3.82(m,1H)
12	CF_3CH_2-		R	3265,1676,1642, 1337,1161 (Nujol)	2.2-2.7(m,2H),3.99(t,J=7.0Hz,1H)
13			RS	3403,3261,1669, 1321,1160	1.68(m,2H), 2.37(m,2H), 3.64(t, J=6.9Hz,1H)
14			R	3302,1667,1324, 1153(Nujol)	2.71(dd,J=7.0,14.4Hz,1H), 2.96(dd, J=7.0,14.2Hz,1H),3.78(t,J=7.6Hz, 1H)
15			S	3406,1670,1582, 1325,1153	2.71(dd,J=7.9,14.4Hz,1H),2.96(dd, J=7.6,14.4Hz,1H),3.78(dd,J=7.2, 7.3Hz,1H)
16	$(CH_3)_2CH$-		R	3268,1634,1584, 1336,1157	0.76(d,J=6.6Hz,6H), 1.77(m,1H), 3.26(m,1H)
17		$CH_3(CH_2)_7$—	R	3700-2400br,1663, 1320,1145 (film)	0.87(t,J=6.3Hz,3H),2.50(t,J=7.4Hz,2H),2. 76(dd,J=9.6,14.0Hz,1H),2.87(dd,J=5.8,14 .0Hz,1H),3.84(dd,J=5.8,9.6Hz,1H),

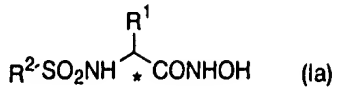
[Table 5]



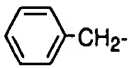
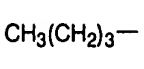
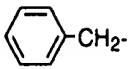
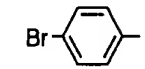
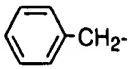
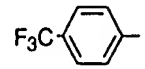
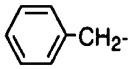
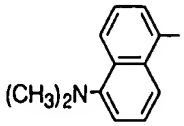
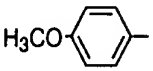
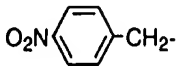
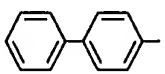
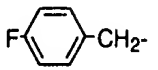
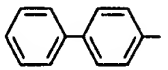
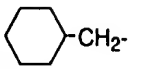
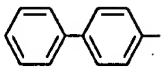
(Ia)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
18			R	oil	——
19			R	144-146	$C_{15}H_{15}N_2BrO_4S$·00.2Ether Calc. C;45.83 H;4.14 N;6.77 Foun.C;45.66 H;3.96 N;6.59
20			R	116-118	——
21			R	91-92	——
22	$(CH_3)_2CH$—		R	178-179	$C_{12}H_{18}N_2O_5S$ Calc. C;47.67 H;6.00 N;9.27 S;10.60 Foun.C;47.68 H;5.98 N;9.28 S;10.76
23			RS	184-185	$C_{21}H_{19}N_3O_6S$·00.2H_2O Calc. C;56.67 H;4.39 N;9.44 S;7.20 Foun.C;56.56 H;4.46 N;9.76 S;7.16
24			RS	128-130	$C_{21}H_{19}N_2FO_4S$·00.4H_2O Calc. C;59.82 H;4.79 N;6.64 F;4.51 S;7.60 Foun.C;59.83 H;4.65 N;6.75 F;4.36 S;7.62
25			R	165-166	$C_{21}H_{26}N_2O_4S$ Calc. C;62.66 H;6.51 N;6.96 S;7.97 Foun.C;62.57 H;6.57 N;7.15 S;7.87

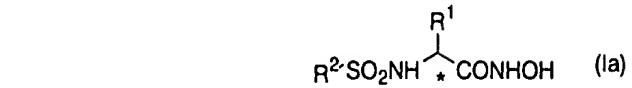
[Table 6]



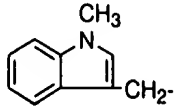
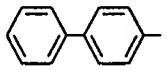
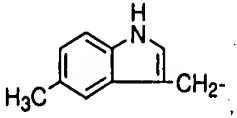
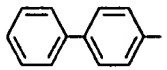
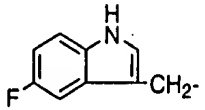
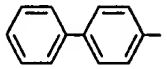
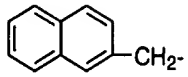
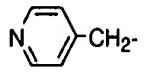
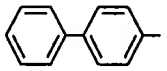
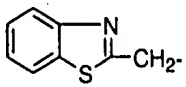
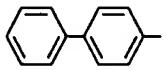
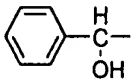
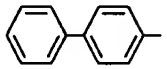
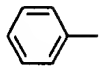
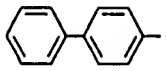
(Ia)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
18			R	3600-2400br,3262,1673, 1321,1142 ($CHCl_3$)	0.79(t,J=7.0Hz,3H),2.32-2.56(m,2H), 2.92(m,1H),3.26(m,1H),
19			R	3700-2200br,3264, 1635,1342,1164,	2.61(dd,J=9.4,13.8Hz,1H),2.78(dd, J=6.0,13.8Hz,1H),3.78(m,1H),7.43 (d,J=8.2Hz,2H),7.60(d,J=8.2Hz,2H),
20			R	3600-2400br,3257, 1743,1721,1323,1132,	2.60-2.82(m,2H),3.84(m,1H),7.00-7.18(m,5H),7.62-7.80(m,4H),
21			R	3700-2100br,3176, 1664,1320,1143,	2.70-2.93(m,2H),2.82(s,6H), 3.75(m,1H),
22	$(CH_3)_2CH$—		R	3268,1632,1598, 1336,1162	0.71(d,J=6.8Hz,3H),0.74(d,J=5.4Hz,3H),1.73 (m,1H),1.73(m,1H),3.22(m,1H),3.82(s,3H),7.05(d,J=9.0Hz,2H),7.69(d,J=9.0Hz,2H)
23			RS	3257,1662,1516, 1344,1322,1160,	2.80(dd,J=10.0,13.8Hz,1H),2.92(dd, J=5.0,12.8Hz,1H),3.90(dd,J=5.4, 9.6Hz,1H),
24			RS	3258,1669,1509, 1322,1157	2.62(dd,J=9.9,13.5Hz,1H),2.78(dd, J=5.8,13.0Hz,1H),3.77(t,J=6.2Hz, 1H),
25			R	3278,2920,1632, 1337,1161	0.50-1.62(m,13H), 3.56(t,J= 7.4Hz,1H)

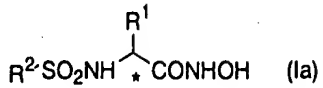
[Table 7]



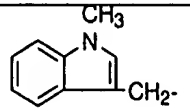
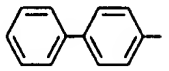
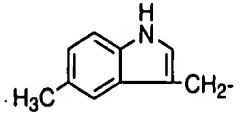
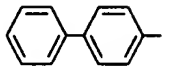
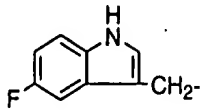
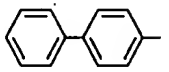
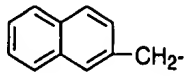
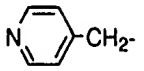
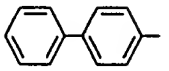
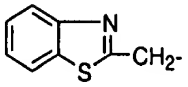
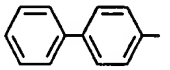
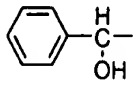
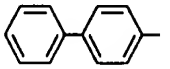
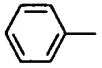
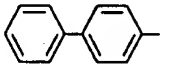
(Ia)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
26			RS	158-163	$C_{24}H_{23}N_3O_4S \cdot 00.15H_2O$ Calc. C;63.74 H;5.19 N;9.29 S;7.09 Foun.C;63.70 H;5.17 N;9.16 S;7.32
27			RS	——	$C_{24}H_{23}N_3O_4S \cdot 00.15H_2O$ Calc. C;63.74 H;5.19 N;9.29 S;7.09 Foun.C;63.53 H;5.20 N;9.12 S;7.18
28			RS	——	$C_{23}H_{20}N_3FO_4S \cdot 00.5H_2O$ Calc. C;59.73 H;4.58 N;9.09 F;4.11 S;6.93 Foun.C;60.02 H;4.46 N;8.92 F;4.12 S;6.75
29			RS	——	——
30			RS	154-158	$C_{20}H_{19}N_3O_4S$ Calc. C;60.44 H;4.82 N;10.57 S;8.07 Foun.C;60.95 H;4.89 N;10.16 S;8.33
31			RS	111-115	$C_{22}H_{19}N_3O_4S_2 \cdot 11.9H_2O$ Calc. C;54.17 H;4.71 N;8.61 S;13.15 Foun.C;54.07 H;4.15 N;8.70 S;12.72
32			RS	——	——
33			R	196-197	$C_{20}H_{18}N_2O_4S$ Calc. C;62.81 H;4.74 N;7.32 S;8.38 Foun.C;62.84 H;4.82 N;7.23 S;8.29

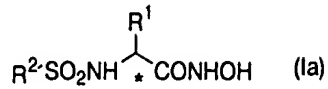
[Table 8]



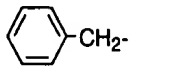
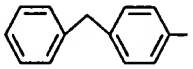
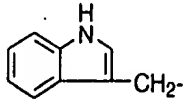
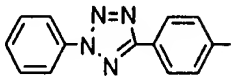
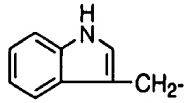
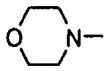
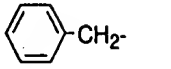
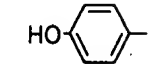
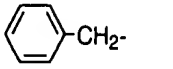
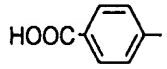
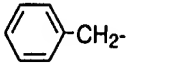
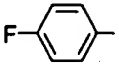
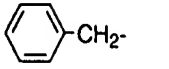
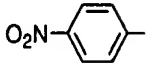
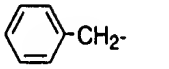
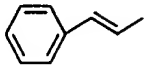
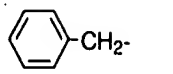
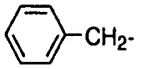
(Ia)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
26			RS	3272,1631,1332, 1161	2.71(dd,J=7.9,14.2Hz,1H),2.94(dd, J=6.9,14.2Hz,1H),3.57(s,3H),3.83 (dd,J=7.0,7.4Hz,1H)
27			RS	3404,1670,1320, 1159	2.25(s,3H),2.67(dd,J=7.5,14.2Hz, 1H),2.95(dd,J=7.7,14.6Hz,1H), 3.81(dd,J=6.2,14.2Hz,1H)
28			RS	3420,1670,1592, 1321,1159	2.72(dd,J=8.0,14.0Hz,1H),2.90(dd, J=6.2,14.2Hz,1H),3.82(m,1H)
29			RS	—	—
30			RS	3186,1593,1480, 1379	2.68(dd,J=9.8,13.7Hz,1H),2.79(dd, J=5.6,12.8Hz,1H),3.85(t,J=7.0Hz,1H),
31			RS	3700-2400br,3252, 1668,1326,1160	3.22-3.38(m,2H),4.17-4.24(m,2H), 7.80(d,J=8.0Hz,2H),7.96(d,J=6.4 Hz,2H)
32			RS	3455,3362,1672, 1398,1162	3.86(d,J=3.6Hz,1H),4.91 (d,J=3.6Hz,1H)
33			R	3404,3315,1669, 1594,1316,1162	4.88(d,J=9.4Hz,1H),8.74(d,J=9.4Hz,1H), 8.98(s,1H),10.92(s,1H)

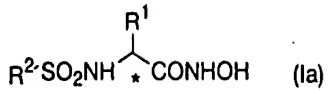
[Table 9]



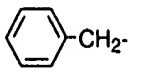
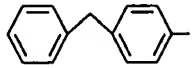
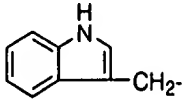
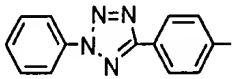
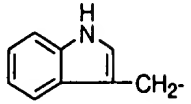
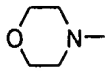
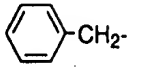
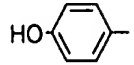
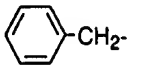
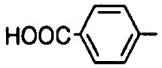
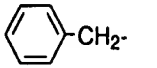
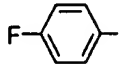
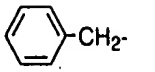
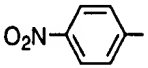
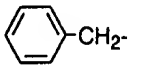
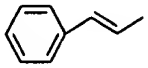
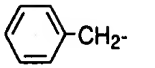
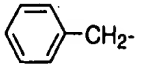
(Ia)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
34			R	85-86	$C_{22}H_{22}N_2O_4S \cdot 00.3H_2O$ Calc. C;63.54 H;5.48 N;6.74 S;7.71 Foun.C;63.65 H;5.38 N;6.68 S;7.53
35			R	——	——
36			R	——	——
37			R	197-199	$C_{15}H_{16}N_2O_5S$ Calc. C;53.56 H;4.79 N;8.33 S;9.53 Foun.C;54.05 H;5.02 N;8.26 S;9.16
38			R	201-202	——
39			R	63-65	——
40			R	70-71	——
41			R	138-139	$C_{17}H_{18}N_2O_4S \cdot 00.5H_2O$ Calc. C;57.45 H;5.39 N;7.88 S;9.02 Foun.C;57.49 H;5.10 N;7.58 S;8.66
42			R	69-70	$C_{16}H_{18}N_2O_4S \cdot 00.3Ethylether$ Calc. C;57.93 H;5.94 N;7.85 S;8.99 Foun.C;58.08 H;5.54 N;7.29 S;9.09

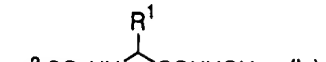
[Table 10]



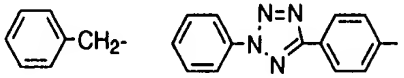
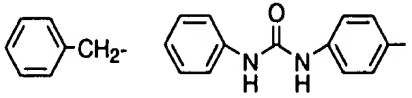
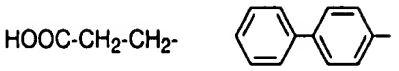
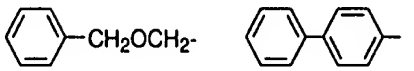
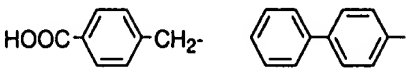
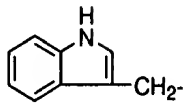
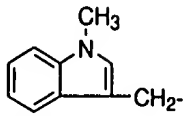
(Ia)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
34			R	3700-2200(br),3262, 1639,1332,1156	2.80(m,1H),2.96(m,1H),3.94(s,2H),3.86(m, 1H),6.80-7.52(m,10H),7.08(A_2B_2qJ=7.5Hz, 2H),7.42(A_2B_2q,J=7.5Hz,2H)($CDCl_3$)
35			R	—	—
36			R	—	—
37			R	3700-2400(br),3473, 1675,1310,1152	2.69(dd,J=7.6,13.5Hz,1H),2.93(dd,J=7.6,13.5 Hz,1H),3.77(t,J=7.6Hz,H),(CD_3OD)
38			R	3700-2200(br),3278, 1706,1645,1322,1162	2.74(dd,J=8.3,13.5Hz,1H),2.95(dd,J=6.5,13.5H z,1H),3.87(dd,J=6.5,8.3Hz,1H),(CD_3OD)
39			R	3700-2200(br),3362,1670, 1590,1336,1152	2.60(dd,J=9.0,13.8Hz,1H),2.79(dd, J=9.3,13.8Hz,lH),3.76(m,1H)
40			R	3700-2200br,3372,1674, 1531,1348,1310,1161	2.66(dd,J=9.5,13.6Hz,1H),2.79(dd,J=5.4,13.6Hz,1H), 3.84(m,1H),7.73(A_2B_2qJ=8.9Hz,2H),8.20(A_2B_2q,J=8. 9Hz,2H),8.72(d,J=9.0Hz,1H),8.86(s,1H),10.7(s,1H)
41			R	3700-2400(br),3312, 1629,1329,1144	2.79(dd,J=8.5,13.4Hz,1H),2.89(dd,J=6.0,13.4Hz,1 H),3.81(dd,J=6.0,8.5Hz,1H),6.55(d,J=15.5Hz,1H)
42			R	3700-2200(br),1670, 1318,1152	2.78(dd,J=8.6,13.4Hz,1H),2.91(dd,J=6.0,13.4Hz,1 H),3.92(ABq,J=13.5Hz,1H),3.90(m,1H),9.01(s,1H), 10.78(s,1H)

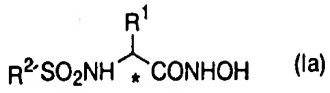
[Table 11]



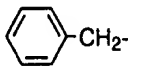
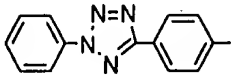
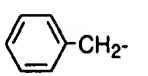
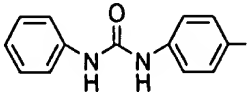
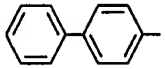
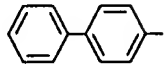
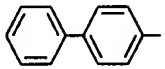
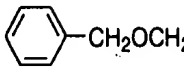
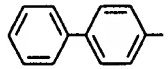
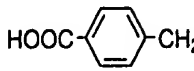
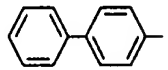
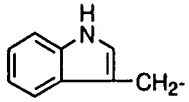
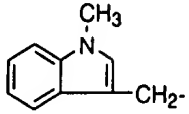
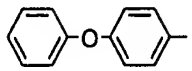
(Ia)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
43			R	194-195	$C_{22}H_{20}N_6O_4S$ Calc. C;56.89 H;4.34 N;18.09 S;6.90 Foun.C;56.88 H;4.47 N;17.67 S;6.76
44			R	206-207	$C_{22}H_{22}N_4O_5S$ Calc. C;58.14 H;4.88 N;12.33 S;7.06 Foun.C;57.91 H;4.91 N;12.00 S;6.87
45			R	——	——
46			R	——	——
47			R	192-193	$C_{15}H_{16}N_2O_5S \cdot 00.4H_2O$ Calc. C;52.44 H;4.93 N;8.15 S;9.33 Foun.C;52.40 H;4.89 N;7.95 S;9.28
48			R	69-70	$C_{22}H_{22}N_2O_5S$ Calc. C;61.96 H;5.20 N;6.57 S;7.52 Foun.C;61.86 H;5.33 N;6.40 S;7.33
49			R	——	——
50			R	160-162	$C_{17}H_{17}N_2O_4S \cdot 00.2H_2O$ Calc. C;56.25 H;4.83 N;11.58 S;8.83 Foun.C;56.47 H;5.03 N;11.73 S;8.38
51			RS	——	——

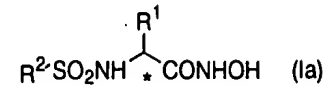
[Table 12]



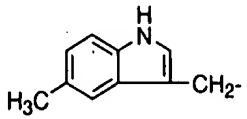
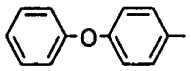
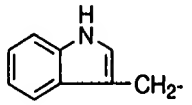
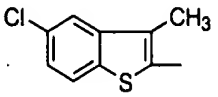
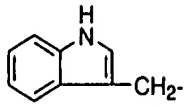
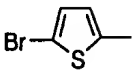
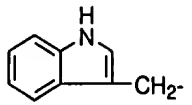
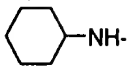
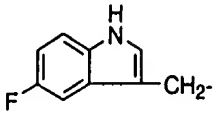
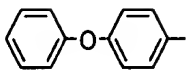
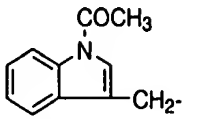
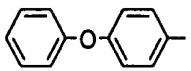
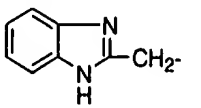
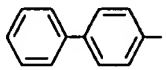
(Ia)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
43			R	3700-2200(br),3278, 1634,1337,1160	2.65(dd,J=9.3,13.1Hz,1H),2.82(dd, J=5.8,13.1Hz,1H),3.86(dt,J=5.8,9.3 Hz,1H),7.72(A_2B_2q,J=8.1Hz,2H), 8.19(A_2B_2q,J=8.1Hz,2H),8.49(d,J= 9.3Hz,1H),8.88(s,1H),10.69(s,1H)
44			R	3700-2400(br),3357,1686, 1641,1314,1155	2.57(dd,J=8.3,13.6Hz,1H),2.79(dd,J=6.0,13.6Hz,1H),3.76(m,1H),8.02(d,J=8.7Hz,1H),8.80(s,1H),8.85(d, J=1.7Hz,1H),9.06(s,1H),10.59(d,J=1.7Hz,1H)
45	HOOC-CH_2-		R	——	——
46	HOOC-CH_2-CH_2-		R	——	——
47	HOCH_2-		R	3700-2400(br),3392, 1667,1320,1161	3.29(dd,J=5.7,10.7Hz,1H),3.43(dd,J=8. 4,10.7Hz,1H),3.62(m,1H),7.85(A_2B_2q,J =8.7Hz,2H),7.88(A_2B_2q,J=8.7Hz,2H),7. 98(d,J=7.8Hz,1H),10.61(s,1H)
48			R	3700-2200(br),1671, 1329,1163	3.31(m,1H),3.46(dd,J=6.8,9.3Hz, 1H),3.89(t,J=6.8Hz,1H),4.33(ABq, J=12.3Hz,2H),
48			R	——	——
50			R	3401,3260,1673, 1316,1165	2.66(dd,J=7.5,13.4Hz,1H),2.96(dd, J=7.6,14.2Hz,1H),3.81(m,1H)
51			RS	3314,1669,1582, 1420,1328,1154	2.71(dd,J=7.9,14.2Hz,1H),2.93(dd, J=6.5,14.3Hz,1H),3.65(s,3H),3.78 (dd,J=7.1,7.2Hz,1H)

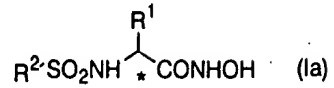
[Table 13]



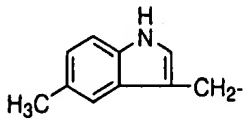
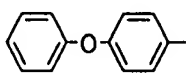
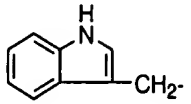
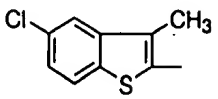
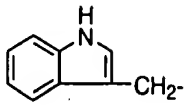
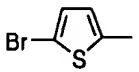
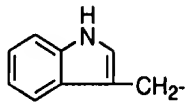
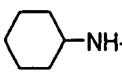
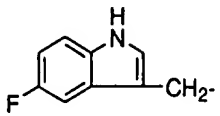
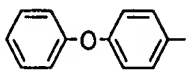
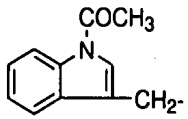
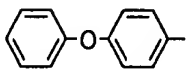
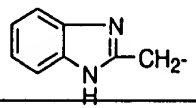
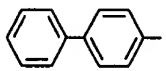
(Ia)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
52			RS	——	——
53			R	——	——
54			R	——	——
55			R	——	——
56			RS	——	——
57			RS	——	$C_{25}H_{23}N_3O_6S \cdot 00.3H_2O$ Calc. C;60.18 H;4.77 N;8.42 S;6.43 Foun.C;60.26 H;5.00 N;8.20 S;6.19
58			RS	141-145	$C_{22}H_{20}N_4O_4S \cdot 11.6H_2O$ Calc. C;56.79 H;5.03 N;12.04 S;6.89 Foun.C;57.09 H;5.05 N;11.34 S;6.37

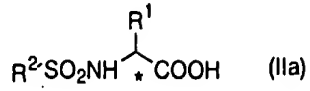
[Table 14]



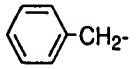
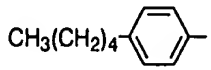
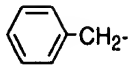
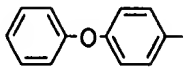
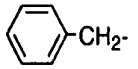
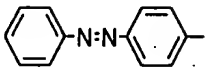
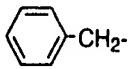
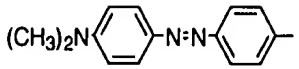
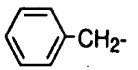
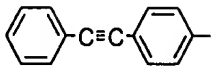
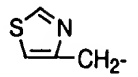
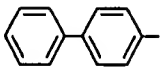
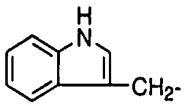
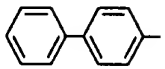
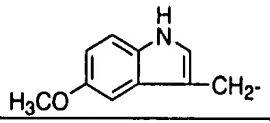
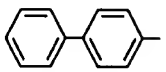
(Ia)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
52			RS	3405,1671,1582, 1487,1324,1154	2.34(s,3H),2.65(dd,J=7.8,14.1Hz, 1H),2.93(dd,J=7.6,14.4Hz,1H), 3.75(dd,J=6.8,7.7Hz,1H)
53			R	—	—
54			R	—	—
55			R	—	—
56			RS	3317,1670,1582, 1488,1323,1153	2.71(dd,J=8.9,14.4Hz,1H),2.89(dd, J=6.6,14.4Hz,1H),3.75(dd,J=6.5, 6.8Hz,1H)
57			RS	3421,1702,1676,1582, 1354,1328,1153	2.54(s,3H),2.69-2.89(m,2H),3.87 (m,1H)
58			RS	3700-2400(br),1672, 1443,1327,1094	2.84-3.21(m,2H),4.29(m,1H)

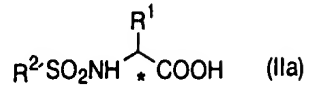
[Table 15]



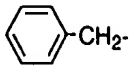
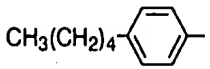
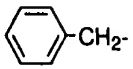
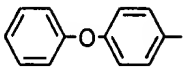
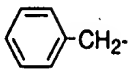
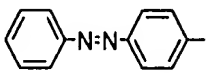
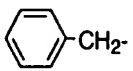
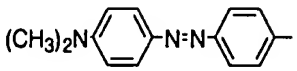
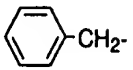
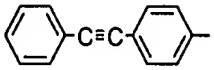
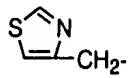
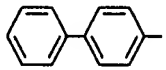
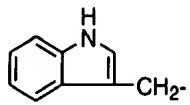
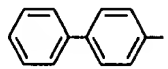
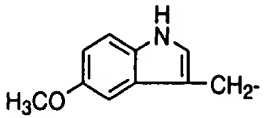
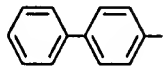
(IIa)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
2			R	121-122	$C_{20}H_{25}NO_4S \cdot 00.3H_2O$ Calc. C;63.67 H;6.77 N;3.68 S;8.42 Foun.C;62.98 H;6.58 N;3.66 S;8.39
3			R	108-109	$C_{21}H_{19}NO_5S$ Calc. C;63.46 H;4.82 N;3.52 S;8.07 Foun.C;63.28 H;4.81 N;3.53 S;7.74
4			R	172-174	$C_{21}H_{19}N_3O_4S \cdot 00.5H_2O$ Calc. C;60.27 H;4.82 N;10.04 S;7.66 Foun.C;60.39 H;4.75 N;9.67 S;7.43
5			R	93-94	$C_{23}H_{24}N_4O_4S \cdot 22CF_3COOH \cdot 00.5H_2O$ Calc. C;47.15 H;3.93 N;8.15 F;16.57 S;4.66 Foun.C;47.35 H;4.21 N;8.25 F;16.07 S;4.21
6			R	176-178	$C_{23}H_{19}NO_4S$ Calc. C;68.13 H;4.72 N;3.45 S;7.91 Foun.C;67.97 H;4.80 N;3.64 S;7.92
7			RS	159-161	$C_{18}H_{16}N_2O_4S_2 \cdot 00.2H_2O$ Calc. C;55.14 H;4.22 N;7.15 S;16.36 Foun.C;55.18 H;4.22 N;7.46 S;16.41
8			R	227-229	$C_{23}H_{20}N_2O_4S \cdot 00.4H_2O$ Calc. C;64.59 H;4.90 N;6.55 S;7.50 Foun.C;64.66 H;5.04 N;6.37 S;7.33
9			RS	181-189	$C_{24}H_{22}N_2O_5S \cdot 11.2H_2O$ Calc. C;61.06 H;5.21 N;5.93 S;6.79 Foun.C;61.24 H;5.20 N;5.75 S;6.26

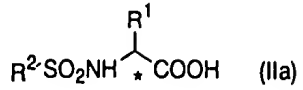
[Table 16]



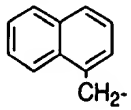
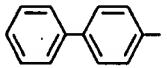
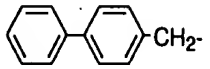
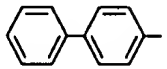
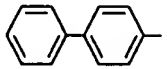
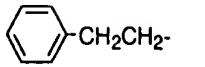
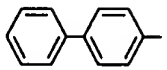
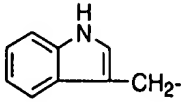
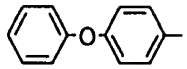
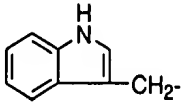
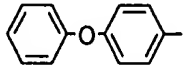
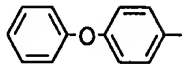
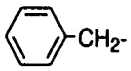
(IIa)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
2			R	2300-3700br,3426,3318, 1713,1330,1159	0.89(t,J=6.7Hz,3H),2.62(t,J=7.6Hz,2H),2.96(dd,J =7.0,13.9Hz,1H),3.10(dd,J=5.4,13.9Hz,1H),4.19 (dt,J=6.9,8.2Hz,1H),5.30(d,J=8.2Hz,1H),
3			R	2400-3600br,3345,3213, 1735,1700,1346,1163	2.72(dd,J=8.7,13.6Hz,1H),2.94(dd, J=5.6,13.6Hz,1H),3.84(ddd,J=5.6, 8.7,8.7Hz,1H),8.23(d,J=8.7Hz,1H)
4			R	2400-3600br,3426,3296, 1698,1350,1167	2.75(dd,J=9.1,13.7Hz,1H),2.98(dd, J=5.5,13.7Hz,1H),3.96(ddd,J=5.5, 9.1,9.1Hz,1H),8.51(d,J+9.1Hz,1H)
5			R	2200-3700br,3431, 1735,1391,1154	2.74(dd,J=9.1,13.6Hz,1H),2.96(dd,J=5 .7,13.6Hz,1H),3.09(s,6H),3.93(dt,J=5. 7,9.1Hz,1H),8.39(d,J=9.1Hz,1H)
6			R	2200-3700br,3430, 3292,1728,1324,1162	2.73(dd,J=9.3,13.6Hz,1H),2.96(dd, J=5.4,13.5Hz,1H),3.92(dt,J=5.4, 9.3Hz,1H),8.42(d,J=9.3Hz,1H)
7			RS	3276,2503br,1897br, 1724,1344,1170(Nujol)	2.95(dd,J=9.0,14.0Hz,1H),3.12(dd,J =5.4,14.0Hz,1H),4.13(m,1H),7.29(d, J=2.0Hz,1H),8.34(d,J=8.6Hz,1H),8. 88(d,J=2.0Hz,1H),12.79(br,1H)
8			R	3386,3305,1747,1363, 1323,1161,1135(Nujol)	2.88(dd,J=8.0,14.0Hz,1H),3.09(dd, J=6.0,14.0Hz,1H),3.91(m,1H),8.23 (m,1H),10.79(s,1H),12.70(br,1H)
9			RS	2400-3700(br),1734, 1484,1327,1160	2.75-3.06(m,2H),3.69(s,3H),3.90 (m,1H)

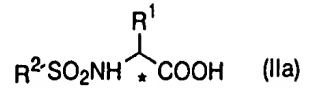
[Table 17]



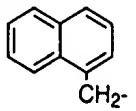
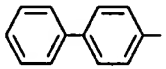
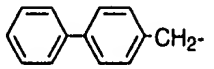
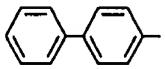
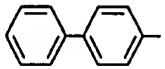
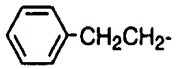
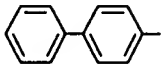
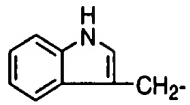
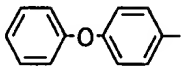
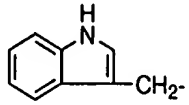
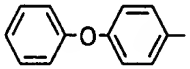
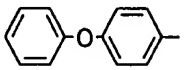
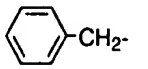
(IIa)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
10			RS	198-200	$C_{25}H_{21}NO_4S \cdot 00.2H_2O$ Calc. C;69.01 H;4.96 N;3.32 S;7.37 Foun.C;68.87 H;5.02 N;3.36 S;7.40
11			R	213-215	$C_{27}H_{23}NO_4S$ Calc. C;70.88 H;5.07 N;3.06 S;7.01 Foun.C;70.66 H;5.20 N;3.34 S;7.13
12	CF_3CH_2-		R	176-177	——
13			RS	153-156	$C_{22}H_{21}NO_4S \cdot 00.2H_2O$ Calc. C;66.21 H;5.40 N;3.51 S;8.03 Foun.C;66.06 H;5.49 N;3.93 S;8.25
14			R	82-87	$C_{23}H_{20}N_2O_5S$ Calc. C;63.29 H;4.62 N;6.42 S;7.35 Foun.C;63.04 H;4.74 N;6.16 S;7.06
15			S	foam	$C_{23}H_{20}N_2O_5S \cdot 00.4H_2O$ Calc. C;62.26 H;4.73 N;6.31 S;7.23 Foun.C;62.47 H;5.02 N;5.88 S;7.11
16	$(CH_3)_2CH$-		R	137-138	$C_{17}H_{19}NO_5S \cdot 00.2H_2O$ Calc. C;57.84 H;5.54 N;3.97 S;9.08 Foun.C;57.80 H;5.44 N;4.11 S;8.95
17		$CH_3(CH_2)_7$—	R	oil	$C_{17}H_{27}NO_4S \cdot 00.3H_2O$ Calc. C;58.87 H;8.02 N;4.04 S;9.24 Foun.C;58.91 H;8.01 N;3.91 S;9.10

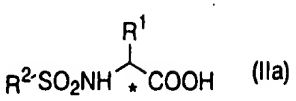
[Table 18]



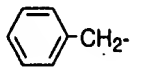
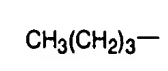
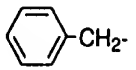
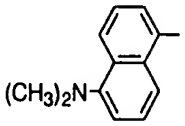
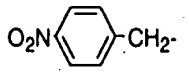
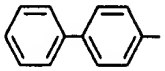
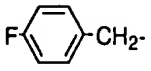
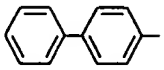
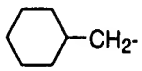
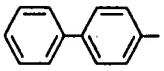
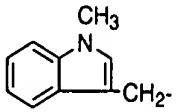
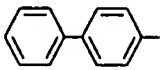
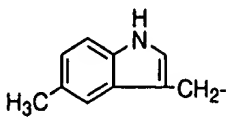
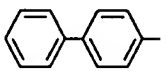
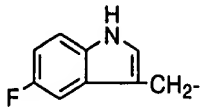
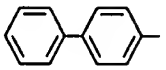
(IIa)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
10			RS	3446,3065,1594,1397, 1303,1154,1094	3.17(dd,J=7.4,13.8Hz,1H),3.57(dd, J=5.5,13.9Hz,1H),3.80(t,J=5.6Hz, 1H),8.11(d,J=7.4Hz,1H)
11			R	3184,1723,1337, 1317,1156	2.77(dd,J=9.7,13.7Hz,1H),3.03(dd, J=4.9,13.3Hz,1H),3.93(m,1H),8.38 (d,J=8.8Hz,1H)
12	CF_3CH_2-		R	3276,1706,1344, 1260,1165	2.40-2.90(m,2H),4.05(m,1H),8.51 (d,J=9.0Hz,1H),13.2(br,1H)
13			RS	3289,1739,1326, 1159,1089	1.83(m,2H),2.52(m,2H),3.70(m, 1H),8.32(d,J=9.0Hz,1H)
14			R	3410,3276,1724,1582, 1488,1331,1152(Nujol)	2.88(dd,J=7.4,15.2Hz,1H),3.07(dd, J=6.2,14.4Hz,1H),3.83(m,1H),8.08 (m,1H),10.80(s,1H),12.70(br,1H)
15			S	3412,1724,1582,1488, 1332,1152	2.81-3.12(m,2H),3.88(m,1H),8.19 (d,J=8.4Hz,1H)
16	$(CH_3)_2CH$-		R	3154,1720,1688,1583, 1488,1251	0.89(d,J=7.0Hz,3H),0.98(d.J=6.8 Hz,3H),2.12(m,2H),3.80(dd,J=4.7 ,9.7Hz,1H),5.17(d,J=9.6Hz,1H)
17		$CH_3(CH_2)_7$—	R	2400-3600br,3340,1736, 1334,1142($CHCl_3$)	0.88(t,J=6.9Hz,3H),2.55-2.73(m,2H),2.97(dd,J=8.4,13.8Hz,1H),3.24(dd,J=4.8,13.8H z,1H),4.35(m,1H),4.98(m,1H) ($CDCl_3$)

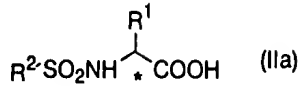
[Table 19]



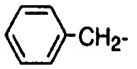
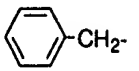
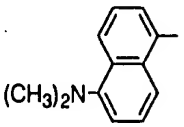
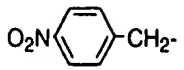
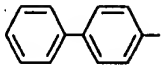
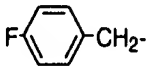
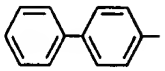
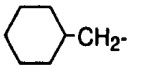
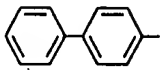
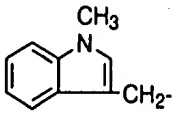
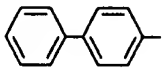
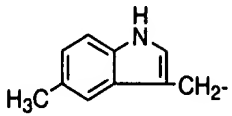
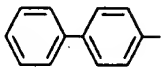
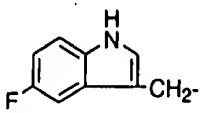
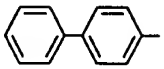
(IIa)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
18			R	89-90	$C_{13}H_{19}NO_4S \cdot 00.4H_2O$ Calc. C;53.37 H;6.82 N;4.79 S;10.96 Foun.C;53.55 H;6.96 N;4.96 S;10.91
21			R	103-105	$C_{21}H_{22}N_2O_4S \cdot 00.4H_2O$ Calc. C;62.17 H;5.66 N;6.91 S;7.90 Foun.C;62.36 H;5.84 N;6.71 S;7.75
23			RS	212-213	$C_{21}H_{18}N_2O_6S \cdot 00.1H_2O$ Calc. C;58.90 H;4.28 N;6.54 S;7.49 Foun.C;58.72 H;4.35 N;6.72 S;7.59
24			RS	164-165	$C_{21}H_{18}NFO_4S$ Calc. C;63.14 H;4.54 N;3.51 F;4.76 S;8.03 Foun.C;62.93 H;4.53 N;3.71 F;4.66 S;8.13
25			R	85-87	——
26			RS	179-183	$C_{24}H_{22}N_2O_4S$ Calc. C;66.34 H;5.10 N;6.45 S;7.38 Foun.C;66.33 H;5.13 N;6.30 S;7.36
27			RS	115-120	$C_{24}H_{22}N_2O_4S$ Calc. C;66.34 H;5.10 N;6.45 S;7.38 Foun.C;66.13 H;5.64 N;5.97 S;6.88
28			RS	208-211	$C_{23}H_{19}N_2FO_4S \cdot 00.2H_2O$ Calc. C;62.49 H;4.42 N;6.34 F;4.30 S;7.38 Foun.C;62.38 H;4.62 N;6.35 F;4.13 S;7.31

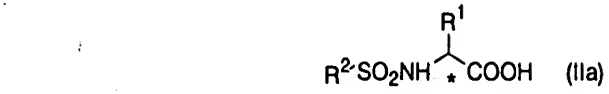
[Table 20]



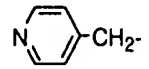
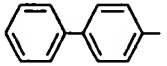
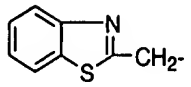
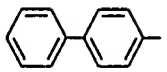
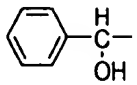
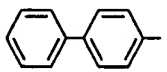
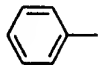
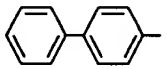
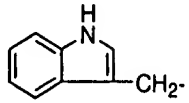
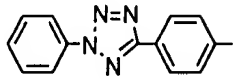
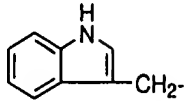
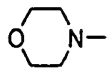
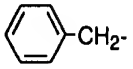
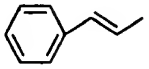
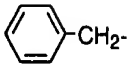
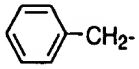
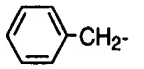
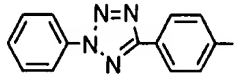
(IIa)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
18		$CH_3(CH_2)_3$—	R	2300-3700br,3240, 1725,1341,1144	0.84(t,J=7.1Hz,3H),2.57-2.70(m,2H),2.97(dd, J=8.4,13.9Hz,1H),3.25(dd,J=4.8,13.9Hz,1H), 4.35(m,1H),4.96(d,J=9.6Hz,1H) ($CDCl_3$)
21			R	2200-3700br,3439,3288, 1725,1329,1143	2.86(m,1H),2.87(s,6H),2.98(dd,J= 5.1,13.8Hz,1H),4.15(m,1H),5.54 (m,1H)
23			RS	3113,1724,1520, 1345,1158	2.86(dd,J=10.2,13.2Hz,1H), 3.14(dd,J=4.5,13.7Hz,1H), 4.02(m,1H),8.42(d,J=8.4Hz,1H)
24			RS	3426,3114,1715, 1509,1224,1159	2.71(dd,J=9.9,13.7Hz,1H),2.96(dd, J=5.3,13.5Hz,1H),3.89(m,1H), 8.34(d,J=9.0Hz,1H)
25			R	2919,1688,1448, 1335,1326,1169	0.52-1.72(m,13H),3.68(m,1H), 8.20(br.s,1H)
26			RS	3432,3294.1713, 1482,1341,1159	2.80-3.12(m,2H),3.61(s,3H), 3.94(m,1H),8.30(d,J=8.6Hz,1H)
27			RS	3419,3397,3291,1736, 1482,1336,1321,1165	2.28(s,3H),2.78-3.10(m,2H),3.91 (m,1H),8.29(d,J=8.3Hz,1H)
28			RS	3407,3285,1751,1735, 1703,1486,1321,1162	2.80-3.10(m,2H),3.92(m,1H), 8.29(d,J=8.2Hz,1H)

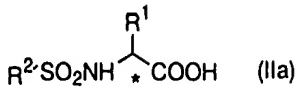
[Table 21]



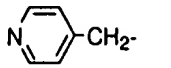
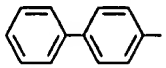
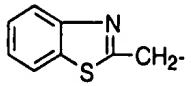
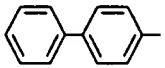
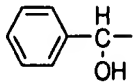
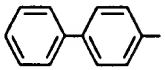
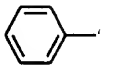
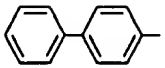
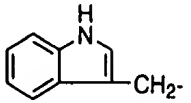
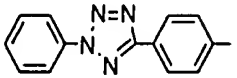
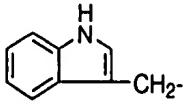
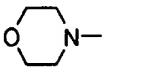
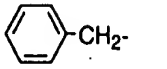
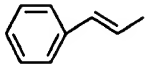
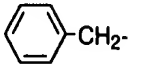
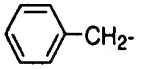
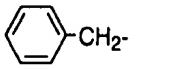
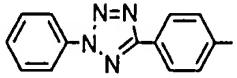
(IIa)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
30			RS	197-205	——
31			RS	196-199	$C_{22}H_{18}N_2O_4S_2 \cdot 00.2H_2O$ Calc. C;59.77 H;4.19 N;6.34 S;14.50 Foun.C;59.65 H;4.24 N;6.43 S;14.51
32			RS	141-143	$C_{21}H_{19}NO_5S \cdot 00.2H_2O$ Calc. C;62.89 H;4.88 N;3.49 S;7.99 Foun.C;62.75 H;4.84 N;3.66 S;7.98
33			R	211-214	$C_{20}H_{17}NO_4S$ Calc. C;65.38 H;4.66 N;3.81 S;8.73 Foun.C;65.09 H;4.76 N;3.72 S;8.50
35			R	205-207	——
36			R	foam	——
41			R	116-117	$C_{17}H_{17}NO_4S \cdot 00.2H_2O$ Calc. C;60.95 H;5.24 N;4.18 S;9.57 Foun.C;60.97 H;5.21 N;4.34 S;9.42
42			R	foam	$C_{16}H_{17}NO_4S \cdot 00.2H_2O$ Calc. C;59.50 H;5.43 N;4.34 S;9.93 Foun.C;59.83 H;5.83 N;4.24 S;9.24
43			R	215-216	$C_{22}H_{19}N_5O_4S \cdot 00.5H_2O$ Calc. C;57.63 H;4.40 N;15.27 S;6.99 Foun.C;57.72 H;4.38 N;15.02 S;6.84

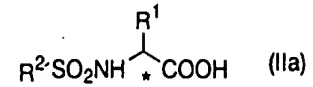
[Table 22]



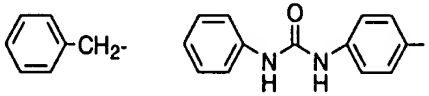
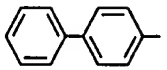
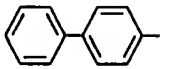
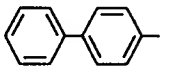
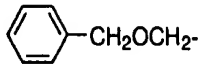
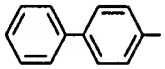
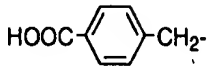
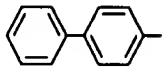
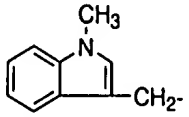
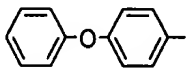
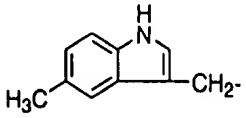
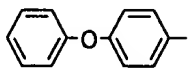
(IIa)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
30			RS	2600-3700br,1635,1594, 1335,1163,1095	2.60-3.04(m,2H),3.98(m,1H)
31			RS	2200-3700br,1713br, 1345,1125	3.24-3.56(m,2H),4,34(m,1H)
32			RS	3335,3246,1732, 1315,1152	4.10(d.J=3.2Hz,1H),5.13(d,J= 3.2Hz,1H)
33			R	3316,1734,1325, 1159(Nujol)	4.94(d,J=9.4Hz,1H),8.80(d,J= 9.4Hz,1H),13.0(br.s,1H)
35			R	3413,1594,1456, 1416,1157	3.03(dd,J=6.5,15.1Hz,1H),3.15 (dd,J=4.7,14.1Hz,1H),3.64(t, J=5.1Hz,1H),10.68(s,1H)
36			R	3412,2859,1589,1420, 1338,1149	2.98(dd,J=7.0,14.8Hz,1H),3.15 (dd,J=4.4,14.0Hz,1H),3.78(m, 1H),10.77(s,1H)
41			R	2400-3700br,3252,1765, 1725,1301,1140	2.81(dd,J=9.2,13.7Hz,1H),3.03(dd,J=5.4,13.7Hz, 1H),3.94(dt,J=5.4,9.2Hz,1H),6.66(d,J=15.2Hz,1H),7.16(d,J=15.2Hz,1H),8.01(d,J=9.2Hz,1H)
42			R	2200-3700br,3268,1726, 1321,1152(film)	2.81(dd,J=9.2,13.7Hz,1H),3.00(dd,J=5 .6,13.7Hz,1H),4.01(ABq,J=13.7Hz,2H) ,4.01(m,1H),7.65(d,J=8.3Hz,1H)
43			R	2400-3700br,3422,3337, 1733,1698,1347,1170	2.75(dd,J=9.3,13.7Hz,1H),2.99(dd,J=5.3 ,13.7Hz,1H),3.96(dt,J=5.3,9.3Hz,1H),8. 53(d,J=9.3Hz,1H)

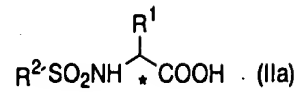
[Table 23]



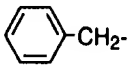
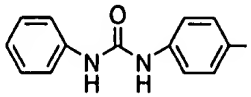
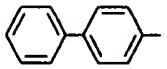
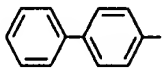
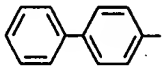
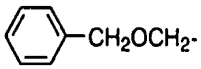
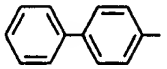
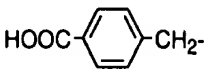
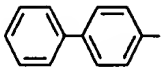
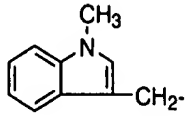
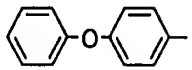
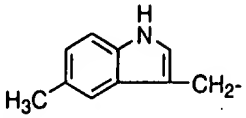
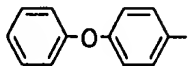
(IIa)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
44			R	203-204	$C_{22}H_{21}N_3O_5S$ Calc. C;60.12 H;4.82 N;9.56 S;7.30 Foun.C;59.72 H;4.87 N;9.50 S;7.15
45	HOOC-CH_2-		R	171-173	$C_{16}H_{15}NO_6S \cdot 00.4H_2O$ Calc. C;53.90 H;4.47 N;3.93 S;8.99 Foun.C;53.96 H;4.51 N;3.94 S;8.62
46	HOOC-CH_2-CH_2-		R	185-187	$C_{17}H_{17}NO_6S \cdot 00.6H_2O$ Calc. C;54.57 H;4.90 N;3.74 S;8.57 Foun.C;54.55 H;5.07 N;3.96 S;8.35
47	HOCH_2-		R	277-279	$C_{15}H_{15}NO_5S \cdot 00.6H_2O$ Calc. C;54.24 H;4.92 N;4.22 S;9.65 Foun.C;54.16 H;4.60 N;4.08 S;9.74
48			R	89-91	——
49			R	>270	$C_{22}H_{19}NO_6S \cdot 00.2H_2O$ Calc. C;61.59 H;4.56 N;3.26 S;7.47 Foun.C;61.49 H;4.55 N;3.41 S;7.45
51			RS	——	$C_{24}H_{22}N_2O_5S \cdot 00.4H_2O$ Calc. C;62.98 H;5.02 N;6.12 S;7.01 Foun.C;63.07 H;5.14 N;6.14 S;6.69
52			RS	——	$C_{24}H_{22}N_2O_5S \cdot 00.5H_2O$ Calc. C;62.73 H;5.04 N;6.10 S;6.98 Foun.C;62.75 H;5.15 N;6.02 S;6.60

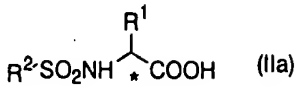
[Table 24]



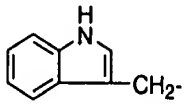
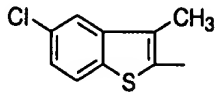
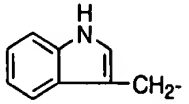
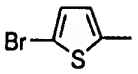
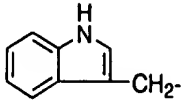
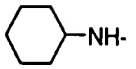
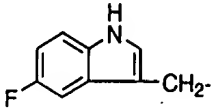
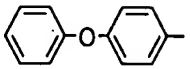
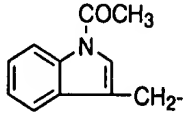
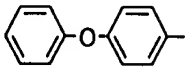
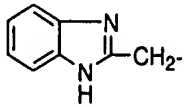
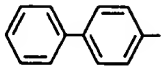
(IIa)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
44			R	2300-3700br,3358, 3262,1718,1686, 1660,1313,1159	2.71(dd,J=9.1,13.7Hz,1H),2.93(dd,J=5.6, 13.7Hz,1H),3.84(dt,J=5.6,9.1Hz,1H),8.11(d,J=9.1Hz,1H),8.78(s,1H),9.06(s,1H)
45	HOOC-CH_2-		R	3353,1752,1326, 1155,1096	2.45(dd,J=6.2,16.4Hz,1H)2.63(dd, J=6.6,16.4Hz,1H),
46	HOOC-CH_2-CH_2-		R	3270.1709,1336, 1159,1093	1.68(dd,J=7.9,14.1Hz,1H),1.87(dd, J=6.0,13.4Hz,1H),2.22(t,J=7.2Hz, 2H),3.80(m,1H),
47	HOCH_2-		R	2200-3700br,3430, 3292,1728,1324,1162	3.51(dd,J=6.0,12.9Hz,1H),3.55(dd, J=5.4,12.9Hz,1H),3.80(m,1H), 8.06(d,J=8.7Hz,1H)
48			R	2200-3700br,3432, 3289,1733,1330,1165	3.54(dd,J=4.8,9.9Hz,1H),3.60(dd, J=5.7,9.9Hz,1H),4.04(m,1H), 4.39(s,2H),8.34(d,J=8.1Hz,1H)
49			R	3319,3052,1701,1317, 1284,1162	2.81(dd,J=9.7,13.7Hz,1H),3.05(dd, J=4.8,13.4Hz,1H),3.96(m,1H), 8.40(d,J=9.0Hz,1H),12.88(br.s,1H)
51			RS	3273,1724,1582,1487. 1331,1198,1153	2.78-3.10(m,2H),3.67(s,3H), 3.86(m,1H)
52			RS	3409,3281,1725,1582, 1331,1197,1153	2.34(s,3H),2.75-3.08(m,2H),3.86(m,1H), 8.19(d,J=8.4Hz,1H)

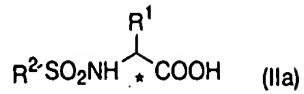
[Table 25]



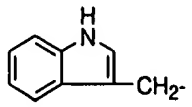
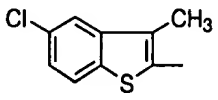
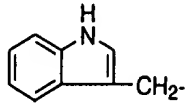
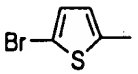
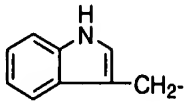
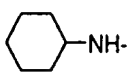
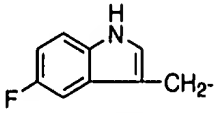
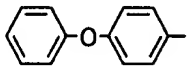
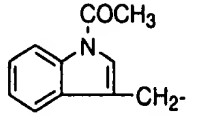
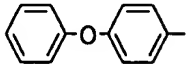
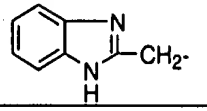
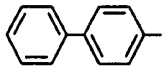
(IIa)

Example No.	R^1	R^2	*	mp. (decomp.) m.pt. (°C)	Elemental analysis
53			R	>250	——
54			R	243-246	——
55			R	——	——
56			RS	——	$C_{23}H_{19}N_2FO_5S \cdot 00.8H_2O$ Calc. C;58.91 H;4.43 N;5.97 F;4.05 S;6.84 Foun.C;59.07 H;4.55 N;5.87 F;3.96 S;6.24
57			RS	236-237	$C_{25}H_{22}N_2O_6S \cdot 00.7H_2O$ Calc. C;61.14 H;4.80 N;5.70 S;6.53 Foun.C;61.13 H;4.59 N;5.73 S;6.66
58			RS	151-156	——

[Table 26]



(IIa)

Example No.	R^1	R^2	*	IR (ν cm^{-1}) (KBr)	^{1}H-NMR (δ ppm) d_6-DMSO
53			R	3421,1580,1333, 1421,1153	2.41(s,3H),3.01(dd,J=6.0,14.4Hz,1H),3.12 (dd,J=4.5,14.4Hz,1H),3.67(t,J=5.4Hz,1H), 6.79(m,1H),6.89(m,1H),10.59(s,1H)
54			R	3420,1588,1402, 1324,1151	3.06(dd,J=5.4,14.4Hz,1H),3.14(dd, J=5.1,14.4Hz,1H),3.65(t,J=5.4Hz, 1H),6.92(m,1H),10.72(s,1H)
55			R	3413,2931,1720,1585, 1455,1421,1313,1144	0.90-1.68(m,9H),1.78(m,1H),2.74 (m,1H),3.00-3.20(m,2H),3.77(m, 1H)6.45(br.s,1H),6.77(br.s,1H)
56			RS	3415,1725,1582,1488, 1329,1196,1174,1152	2.78-3.08(m,2H),3.85(m,1H),8.18 (d,J=8.6Hz,1H)
57			RS	3296,1742,1647,1604, 1581,1342,1334,1152	2.55(s,3H),2.79-3.11(m,2H),3.98 (m,1H)
58			RS	2200-3700br,1734, 1334,1161	3.17-3.50(m,2H),4.51(m,1H)

[0030]

Test examples on the compounds of the present invention are described below. The test compounds are the ones described in the Examples and Tables.

Test example

(1) Isolation and purification of MMP-9 (92 kDa, gelatinase B)

Type IV collagenase (MMP-9) was purified according to the methods descrived in the following literature. Scott M. Wilhelm et al., J. Biol. Chem., 264, 17213-17221, (1989), SV40-transformed Human Lung Fibroblasts Secrete a 92-kDa Type IV Collagenase Which Is Identical to That Secreted by Normal Human Macrophages; Yasunori Okada et al., J. Biol. Chem., 267, 21712-21719, (1992), Matrix Metalloproteinase 9 (92-kDa Gelatinase / Type IV Collagenase) from HT 1080 Human Fibrosarcoma Cells; Robin V. Ward et al., Biochem. J., (1991) 278, 179-187, The purification of tissue inhibitor of metalloproteinase-2 from its 72 kDa progelatinase complex.

MMP-9 is secreted from human fibrosarcoma cell line ATCC HT 1080, into its culture medium when it is stimulated with 12-tetradecanoylphorbol-13-acetate (TPA). The production of MMP-9 in this culture was verified by the gelatin zymography as described in the following literature (Hidekazu Tanaka et al., (1993) Biochem. Biophys. Res. Commun., 190, 732-740, Molecular cloning and manifestation of mouse 105-kDa gelatinase cDNA). The condition medium of the stimulated HT 1080 was concentrated and was purified with gelatin-Sepharose 4B, concanavalin A-sepharose, and Sephacryl S-200. The purified pro-MMP-9 (92 kDa, gelatinase B) thus obtained gave a single positive band in the gelatin zymography. Subsequently, activated MMP-9 was obtained by treating the pro-MMP-9 with trypsin.

[0031]

(2) Assay methods of type IV collagenase inhibitors

Collagenase assay was performed using the activated MMP-9 described above and the substrate supplied in the type IV collagenase activity kit (YAGAI, inc.), according to the manufacturer's protocol. The following 4 assays are performed per compound (inhibitor).

(A) substrate (type IV collagenase), enzyme (MMP-9), inhibitor

(B) substrate (type IV collagenase), inhibitor

(C) substrate (type IV collagenase), enzyme (MMP-9)

(D) substrate (type IV collagenase)

According to the manufacturer's protocol, fluorescent intensity was measured and percent inhibition was determined by the following equation.

Inhibition (%) = {1 - (A - B) / (C - D)} x 100

IC_{50} is a concentration at which the percent inhibition reaches 50 %. The results are shown in Table 27.

[Table 27]

Example No.	Compound No.	IC_{50} (μM)	Compound No.	IC_{50} (μM)
1	Ia-1	0.030	IIa-1	0.24
3	Ia-3	0.0012	IIa-3	1.31
4	Ia-4	0.018	IIa-4	1.2
5	Ia-5	0.0053	IIa-5	0.48
6	Ia-6	0.011	IIa-6	1.5
7	Ia-7	0.040		
8	Ia-8	0.005	IIa-8	0.18
10	Ia-10	0.041	IIa-10	0.81
11	Ia-11	0.034	IIa-11	0.68
12	Ia-12	0.028		
13	Ia-13	0.034	IIa-13	2.0
14	Ia-14	0.0006	IIa-14	0.247
15	Ia-15	0.0005		
16			IIa-16	1.2
24	Ia-24	0.027	IIa-24	3.7
26	Ia-26	0.0108	IIa-26	0.520
27	Ia-27	0.0203	IIa-27	0.205
28	Ia-28	0.0282	IIa-28	0.500
31	Ia-31	0.004		
35	Ia-35		IIa-35	0.048
43	Ia-43	0.0056	IIa-43	0.575
48	Ia-48	0.0129	IIa-48	1.15
51	Ia-51	0.0037	IIa-51	0.520
52	Ia-52	0.0035	IIa-52	0.291
56	Ia-56	0.0041	IIa-56	0.79
58	Ia-58	0.0216		

The compound of the present invention showed strong activity for inhibiting type IV collagenase.

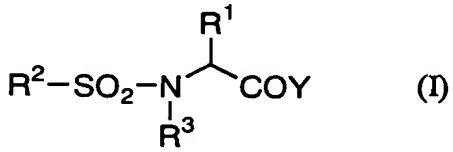
【Document's Name】 Abstract

【Abstract】

【Problem】 Matrix metalloproteinases (MMP) such as gelatinase, stromelysin, collagenase, and the like have an important role in degradation of an extracellular matrix. It is considered that these enzymes participate in progression of diseases such as osteoarthritis, rheumatoid arthritis, corneal ulceration, periodontitis, metastasis and invasion of tumor, and virus infection (for example, HIV infection). Therefore, if it is able to inhibit the activity of MMP, it is considered that MMP inhibitors contribute to an improvement of the above diseases caused by or related to its activity.

【Means for solution】 A compound of the formula (I):

【Formula 1】



(I)

, its pharmaceutically acceptable salt, or hydrate thereof has inhibitory activity against metalloproteinase.

【Representative Drawing】 None

【Document Name】 Official Correction Data

【Corrected Document】 Petition for Patent

【Approved or Supplemented Information】

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Newly Recorded

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state that the attached document is a true and complete translation to the best of my knowledge of Japanese Patent Application No. 30082/96.

Dated this 26th day of April, 1999

Signature of translator : Mitsugu Kiyokawa

Mitsugu Kiyokawa